FORM PTO-1390 (REV 11-2000)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER 1721-45
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) 10/031486 unknown
INTERNATIONAL APPLICATION NO. **PCT/FR00/02122**	INTERNATIONAL FILING DATE **21/07/2000**	PRIORITY DATE CLAIMED **21/07/1999**

TITLE OF INVENTION
QUATERNARY BIS-AMMONIUM SALT PRECURSORS AND THEIR USES AS PRODRUGS HAVING AN ANTIPARASITIC ACTIVITY

APPLICANT(S) FOR DO/EO/US
VIAL, H. et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☒ The U.S. has been elected by the expiration of 19 months from the priority date (Article 31).
5. A copy of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☒ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has **NOT** expired.
   d. ☐ have not been made and will not be made.
8. ☒ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☒ A English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 To 20 below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821-1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information. PTO Form 1449

JC13 Rec'd PCT/PTO 22 JAN 2002

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
unknown 10/031486	PCT/FR00/02122	1721-45

21. ☒ The following fees are submitted: — CALCULATIONS / PTO USE ONLY

BASIC NATIONAL FEE (37 C.F.R. 1.492(a)(1)-(5):

- -- Neither international preliminary examination fee (37 C.F.R. 1.482) nor international search fee (37 C.F.R. 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $1040.00
- -- International preliminary examination fee (37 C.F.R. 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $890.00
- -- International preliminary examination fee (37 C.F.R. 1.482) not paid to USPTO but international search fee (37 C.F.R. 1.445(a)(2)) paid to USPTO $740.00
- -- International preliminary examination fee (37 C.F.R. 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) $710.00
- -- International preliminary examination fee (37 C.F.R. 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) $100.00

ENTER APPROPRIATE BASIC FEE AMOUNT =					$	890.00
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☒ 30 months from the earliest claimed priority date (37 C.F.R. 1.492(e)).					$	130.00
CLAIMS	NUMBER FILED		NUMBER EXTRA	RATE		
Total Claims	23	-20 =	3	X $18.00	$	54.00
Independent Claims	3	-3 =	0	X $84.00		0.00
MULTIPLE DEPENDENT CLAIMS(S) (if applicable)				$280.00	$	280.00
CLAIM FEES ARE NOT BEING PAID AT THIS TIME			**TOTAL OF ABOVE CALCULATIONS =**		$	**1354.00**
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.						0.00
SUBTOTAL =					$	**1354.00**
Processing fee of $130.00, for furnishing the English Translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. 1.492(f)). +						0.00
TOTAL NATIONAL FEE =					$	**1354.00**
Fee for recording the enclosed assignment (37 C.F.R. 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. 3.28, 3.31). **$40.00** per property +					$	0.00
Fee for Petition to Revive Unintentionally Abandoned Application ($1280.00 – Small Entity = $640.00)					$	0.00
TOTAL FEES ENCLOSED =					$	**1354.00**
					Amount to be: refunded	$
					Charged	$

a. ☒ A check in the amount of $1354.00 to cover the above fees is enclosed.
b. ☐ Please charge my Deposit Account No. 14-1140 in the amount of $______ to cover the above fees. A duplicate copy of this form is enclosed.
c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-1140. A duplicate copy of this form is enclosed.
d. ☒ The entire content of the foreign application(s), referred to in this application is/are hereby incorporated by reference in this application.

NOTE: Where an appropriate time limit under 37 C.F.R. 1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

NIXON & VANDERHYE P.C.
1100 North Glebe Road, 8th Floor
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BJSadoff
SIGNATURE

B. J. Sadoff
NAME

36,663 — **January 22, 2002**
REGISTRATION NUMBER — Date

N.V.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

VIAL, H. et al. Atty. Ref.: 1721-45

Serial No. unknown Group:

US National Phase of PCT/GB00/02122

Filed: January 22, 2002 Examiner:

For: QUATERNARY BIS-AMMONIUM SALT PRECURSORS AND THEIR USES AS PRODRUGS HAVING AN ANTIPARASITIC ACTIVITY

* * * * * * * * * * *

January 22, 2002

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

PRELIMINARY AMENDMENT

In order to place the above-identified application in better condition for examination, please amend the application as follows:

IN THE SPECIFICATION

Amend the specification as follows:

Page 1, before the first line, insert as a separate paragraph:

--This application is the US National Phase of International PCT/GB00/02122 filed 21 June 1999, which designated the US.--

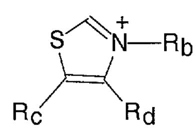
IN THE CLAIMS

Amend the claims as follows:

5. (Amended) Precursors according to claim 2, characterized in that $\underline{R_1}$ is a methyl radical and $\underline{R'_1}$ is either a hydrogen atom, or a methyl radical, and $\underline{W}$ is a chlorine atom.

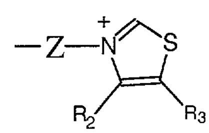
6. (Amended) Precursors according to claim 2, characterized in that they are chosen from N, N'-dimethyl-N,N'-(5-chloropentyl)-1,16-hexadecanediamine hydrochloride, or N, N'-dimethyl-N,N'-(4-chloropentyl)-1,16-hexadecanediamine hydrochloride.

19. (Amended) Pharmaceutical compositions, characterized in that they contain an effective quantity of at least one precursor as defined in claim 1, or at least one cyclized derivative corresponding to precursors of thiazolium of general formula (VI):



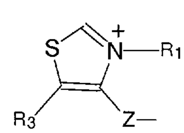
(VI)

in which $\underline{R_b}$ represents $\underline{R_1}$ or $\underline{T}$, $\underline{T}$ representing the group of formula:

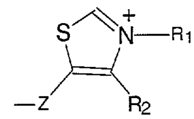


provided that Z does not represent a C1 to C8 alkyl radical, when R_c, R_d, R_1 and R_2 represent a methyl radical.

$\underline{R_d}$ represents $\underline{R_2}$ or $\underline{P}$, $\underline{P}$ representing the group of formula



.$\underline{R_c}$ represents $\underline{R_3}$ or U, U representing the group of formula



$\underline{R_1}$, $\underline{R_2}$, $\underline{R_3}$ and $\underline{Z}$ being as defined in claim 1,

it being understood that $\underline{R_b} = \underline{T}$, if $\underline{R_c} = \underline{R_3}$ and $\underline{R_d} = \underline{R_2}$; $\underline{R_d} = \underline{P}$, if $\underline{R_c} = \underline{R_3}$ and $\underline{R_b} = \underline{R_1}$; and $\underline{R_c} = \underline{U}$, if $\underline{R_b} = \underline{R_1}$, and $\underline{R_d} = \underline{R_2}$.

in combination with a pharmaceutically inert vehicle.

21. (Amended) Pharmaceutical compositions according to claim 19, characterized in this that they can be administered by oral route, by injectable route, or also by rectal route.

REMARKS

The claims have been amended to delete improper multiple dependencies.

The Office is requested to note the pending claims are separately attached as an English translation of the annexes to the IPER.

An early and favorable Action on the merits is requested.

595274

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: ______________________________

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

Page 1, before the first line, insert as a separate paragraph:

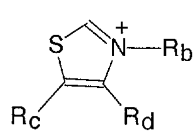
--This application is the US National Phase of International PCT/GB00/02122 filed 21 June 1999, which designated the US.--

IN THE CLAIMS

5. (Amended) Precursors according to [any one of] claim[s] 2 [to 4], characterized in that R_1 is a methyl radical and R'_1 is either a hydrogen atom, or a methyl radical, and W is a chlorine atom.

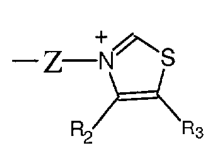
6. (Amended)Precursors according to [any one of]claim[s] 2[to 5], characterized in that they are chosen from N, N'-dimethyl-N,N'-(5-chloropentyl)-1,16-hexadecanediamine hydrochloride, or N, N'-dimethyl-N,N'-(4-chloropentyl)-1,16-hexadecanediamine hydrochloride.

19. (Amended) Pharmaceutical compositions, characterized in that they contain an effective quantity of at least one precursor as defined in [any one of] claim[s] 1[to 13], or at least one cyclized derivative corresponding to precursors of thiazolium of general formula (VI):



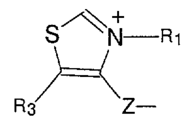
(VI)

in which R_b represents R_1 or T, T representing the group of formula:

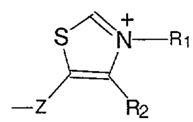


provided that Z does not represent a C1 to C8 alkyl radical, when R_c, R_d, R_1 and R_2 represent a methyl radical.

$\underline{R_d}$ represents $\underline{R_2}$ or $\underline{P}$, $\underline{P}$ representing the group of formula



.$\underline{R_c}$ represents $\underline{R_3}$ or U, U representing the group of formula



$\underline{R_1}$, $\underline{R_2}$, $\underline{R_3}$ and $\underline{Z}$ being as defined in claim 1,

it being understood that $\underline{R_b} = \underline{T}$, if $\underline{R_c} = \underline{R_3}$ and $\underline{R_d} = \underline{R_2}$; $\underline{R_d} = \underline{P}$, if $\underline{R_c} = \underline{R_3}$ and $\underline{R_b} = \underline{R_1}$; and $\underline{R_c} = \underline{U}$, if $\underline{R_b} = \underline{R_1}$ and $\underline{R_d} = \underline{R_2}$.

in combination with a pharmaceutically inert vehicle.

21. (Amended) Pharmaceutical compositions according to claim 19, [or medicaments manufactured according to claim 20,] characterized in this that they can be administered by oral route, by injectable route, or also by rectal route.

6/prts

Precursors of quaternary bis-ammonium salts and their uses as prodrugs with an anti-parasitic action

The invention relates to precursors of quaternary bis-ammonium salts and their uses as prodrugs presenting, in particular, an anti-parasitic, and more especially an anti-malarial action.

The geographic spread of parasitic diseases, and more especially malaria, is considerable.

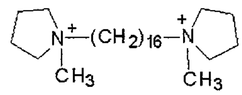
More than 100 countries are affected at present by malaria and more than 2 billion people are exposed to the risk of infection, i.e. nearly half of the world's population (for the malaria situation in the world, see Butler et al, Nature, 1997, 386, 535-540).

The recrudescence of chemically resistant strains of *Plasmodium falciparum* (species deadly to man) in Asia, in Africa and in Latin America is more pertinent than ever and considerably limits the efficacy of the available treatments.

It is therefore considered urgent to have available effective anti-malarial medicaments.

In previous work, some co-inventors of the present Patent Application developed an original pharmacological model capable of preventing the reproduction of the parasite. The compounds synthesized have a quaternary bis-ammonium type structure with a spacer arm, one of the most studied compounds being

constituted by 1,16-hexadecamethylene bis-(N-methylpyrrolidinium), corresponding to the formula



This compound is hereafter called G25.

If such compounds are of considerable interest taking into account the cures that they lead to *in vivo*, without relapse, their action by oral route has, however, proven to be inferior by a factor of at least 100 to that observed by intramuscular route.

Continuation of the work of the inventors to research new compounds presenting an increased efficacy when they are administered by oral route has led them to study a strategy based on the development of neutral prodrugs, *a priori* more easily absorbed, capable of generating *in vivo* the active drug which is present in ionized form.

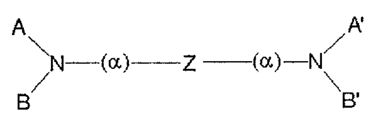
Surprisingly, this work has made it possible to develop very effective prodrugs of quaternary bis-ammonium salts, endowed with a high anti-parasitic action, which are easily absorbed, generating *in vivo* active drugs the bioavailability of which is high.

The invention therefore aims to provide new neutral derivatives, with a high anti-malarial action, which can also be administered by oral route, as well as ionized metabolites generated *in vivo*.

It also relates to a process for synthesizing these prodrugs.

According to yet another aspect, the invention relates to the advantageous use of the properties of these prodrugs for the development of active ingredients of medicaments which can be used for the treatment of parasitic diseases, and in particular malaria and babesiosis in animals or humans.

The precursors of drugs with an anti-malarial action according to the invention are characterized in that they are products capable of generating quaternary bis-ammonium salts and that they correspond to general formula (I)



(I)

*

in which

- <u>A</u> and <u>A'</u> are identical to or different from one another and represent

. either, an <u>A_1</u> and <u>A'_1</u> group respectively of formula

$$-(CH_2)n-\underset{\displaystyle W}{\underset{|}{CH}}-R'_1$$

where <u>n</u> is an integer from 2 to 4; <u>R'_1</u> represents a hydrogen atom, a C1 to C5 alkyl radical, optionally substituted by an aryl (in particular a phenyl radical), a hydroxy, an alkoxy radical, in which the alkyl radical comprises from 1 to 5 C, or aryloxy (in particular phenoxy); and <u>W</u> represents a halogen atom chosen from chlorine, bromine or iodine, or a nucleofuge group, such

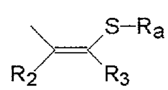
as the tosyl $CH_3-C_6H_4-SO_3$, mesityl CH_3-SO_3, CF_3-SO_3, $NO_2-C_6H_4-SO_3$ radical,

. or an A_2 group which represents a formyl -CHO, or acetyl $-COCH_3$ radical,

- B and B' are identical to or different from one another and represent

. either the B_1 and B'_1 groups respectively, if A and A' represent A_1 and A'_1 respectively, B_1 and B'_1 representing an R_1 group which has the same definition as R'_1 above, but which cannot be a hydrogen atom,

. or the B_2 and B'_2 groups respectively, if A and A' represent A_2, B_2 or B'_2 being the R_1 group as defined above, or a group of formula

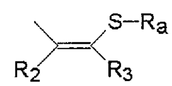


in which -Ra represents an RS- or RCO- group, where R is a linear, branched or cyclic C1 to C6 alkyl radical, in particular C1 to C5, optionally substituted by one or more hydroxy or alkoxy or aryloxy groups or an amino group and/or a -COOH or COOM group, where M is a C1 to C3 alkyl; a phenyl or benzyl radical, in which the phenyl radical is optionally substituted by at least one C1 to C5 alkyl or alkoxy radical, these being optionally substituted by an amino group, or by a nitrogenous or oxygenous heterocycle, a -COOH or -COOM group; or a $-CH_2$-heterocycle group, with 5 or 6 elements, nitrogenous and/or oxygenous; R_2 represents a hydrogen atom, a C1 to C5 alkyl radical, or a $-CH_2-COO$-alkyl (C1 to C5) group; and R_3 represents a hydrogen atom, a C1 to C5 alkyl or

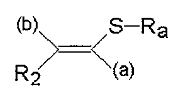
alkenyl radical, optionally substituted by -OH, a phosphate group, an alkoxy radical, in which the alkyl radical is C1 to C3, or aryloxy, or an alkyl (or aryl) carbonyloxy group; or also R_2 and R_3 together form a ring with 5 or 6 carbon atoms; R and R_3 can be linked to form a ring of 5 to 7 atoms (carbon, oxygen, sulphur)

- α represents

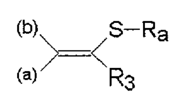
. either a single bond, when A and A' represent A_1 and A'_1: or when A and A' represent A_2 , i.e. a -CHO or $-COCH_3$ group, and B_2 and B'_2 represent



. either, when A and A' represent A_2 and B_2 and B'_2 represent R_1 , a group of formula



or a group of formula



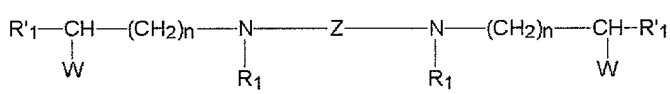
in which (a) represents a bond towards Z and (b) a bond towards the nitrogen atom,

- Z represents a C6 to C21 in particular C13 to C21 alkyl radical, optionally with insertion of one or more multiple bonds, and/or of one or more O and/or S

heteroatoms, and/or one or more aromatic rings, and the pharmaceutically acceptable salts of these compounds.

Except where otherwise specified, "aryl" and "aromatic" as used to define the products of the invention designate a phenyl or any ring, or heterocycle, having an aromatic characteristic such as the pyridine, oxazole, thiazole rings, "alkenyl" designates an alkyl comprising one or more unsaturations, "amino group" designates $-NH_2$ or dialkyl (C_1-C_3) amino, and multiple bond designates an unsaturation (double or triple bond) between 2 carbon atoms.

A preferred group of compounds according to the invention is constituted by the haloalkylamines, precursors of quaternary bis-ammonium salts, which correspond to general formula (II)



(II)

In these compounds, $\underline{R_1}$, $\underline{R'_1}$, $\underline{W}$, $\underline{n}$ and $\underline{Z}$ are as defined above.

In a preferred family of these compounds, $\underline{Z}$ represents a C13 to C21 alkyl radical.

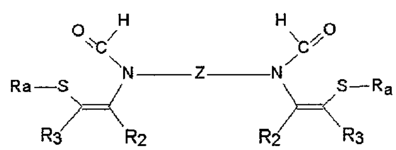
In the preferred derivatives, Z represents a $-(CH_2)_{16}-$ group

In a sub-group of this family, $\underline{R_1}$ is advantageously a methyl radical.

In another sub-group, $\underline{R}_1$ is a methyl radical and $\underline{R'}_1$ is either a hydrogen atom, or a methyl radical, and $\underline{W}$ is a chlorine atom.

Particularly preferred compounds are chosen from N,N'-dimethyl-N,N'-(5-chloropentyl)-1,16-hexadecanediamine dihydrochloride, or N,N'-dimethyl-N,N'-(4-chloropentyl)-1,16-hexadecanediamine dihydrochloride.

Another preferred group of compounds according to the invention is constituted by precursors of thiazolium and correspond to general formula (III)



(III)

in which $\underline{R}_a$, $\underline{R}_2$, $\underline{R}_3$, and $\underline{Z}$ are as defined above.

In a preferred sub-group of this family, $\underline{R}_a$ represents an RCO- radical. Particularly preferred compounds are chosen from

N,N'-diformyl-N,N'-di[1-methyl-2-S-thiobenzoyl-4-methoxybut-1-enyl]-1,12-diaminododecane (designated in the examples by TE4c),

N,N'-diformyl-N,N'-di[1-methyl-2-S-(p-diethylaminomethylphenyl-carboxy)thio-4-methoxybut-1-enyl]-1,12-diaminododecane (TE4f),

N,N'-diformyl-N,N'-di[1-methyl-2-S-(p-morpholino-methylphenylcarboxy)-thio-4-methoxybut-1-enyl]-1,12-diaminododecane (TE4g),

N,N'-diformyl-N,N'-di[1-methyl-2-S-thiobenzoyl-4-methoxybut-1-enyl]-1,16-diaminohexadecane (TE8),

N,N'-diformyl-N,N'-di[1(2-oxo-4,5-dihydro-1,3-oxathian-4-ylidene)ethyl]1,12-diaminododecane (TE3)

In another preferred sub-group, $\underline{R_a}$ represents an <u>RS-</u> radical. Particularly preferred compounds are chosen from

N,N'-diformyl-N,N'-di[1-methyl-2-tetrahydrofurfuryl-methyldithio-4-hydroxybut-1-enyl]-1,12-diaminododecane (TS3a),

N,N'-diformyl-N,N'-di[1-methyl-2-propyl-dithio-4-hydroxybut-1-enyl]-1,12-diaminododecane (TS3b),

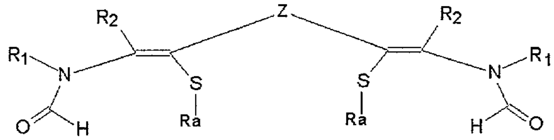
N,N'-diformyl-N,N'-di[1-methyl-2-benzyl-dithio-4-hydroxybut-1-enyl]-1,12-diaminododecane (TS3c),

N,N'-diformyl-N,N'-di[1-methyl-2-(2-hydroxyethyl)-dithio-4-hydroxybut-1-enyl]-1,12-diaminododecane (TS3d)

N,N'-diformyl-N,N'-di[1-methyl-2-propyldithio-4-methoxybut-1-enyl]-1,12-diaminododecane (TS4b),

N,N'-diformyl-N,N'-di[1-methyl-2-propyldithio-ethenyl]-1,12-diaminododecane (TS6b).

Another preferred group of compounds according to the invention is also constituted by precursors of thiazolium salts which correspond to general formula (IV)



(IV)

in which $\underline{R}_a$, $\underline{R}_2$, $\underline{R}_1$ and $\underline{Z}$ are as defined above.

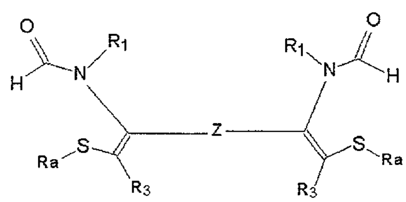
Particularly preferred compounds are chosen from 2,17-(N,N'-diformyl-N,N'-dimethyl)diamino-3,16-S-thio-p-methoxybenzoyl-6,13-dioxaoctadeca-2,16-diene (TE9),

2.17 (N,N'-diformyl-N,N'-dibenzyl)diamino-3,16-S-thio-p-methoxybenzoyl-6,13-dioxaoctadeca-2,16-diene (TE10),

ethyl 3.18 (N,N'-diformyl-N,N'-dimethyldiamino-4,17-S-thiobenzoyl-eicosa-3,17-dienedioate (TE12),

ethyl 3,18-(N,N'-diformyl-N,N'-dibenzyl)diamino-4,17-S-thiobenzoyl-eicosa-3,17-dienedioate (TE13).

Another preferred group of compounds according to the invention is again constituted by precursors of thiazolium salts which correspond to general formula (V)



(V)

in which $\underline{R}_a$, $\underline{R}_3$, $\underline{R}_1$ and Z are as defined above.

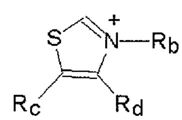
Particularly preferred compounds are chosen from 2,15-(N,N'-diformyl-N,N'-dimethyl)diamino-1,16-S-thio-benzoyl-hexadeca-1,15-diene (TE15),

2,15-(N,N'-diformyl-N,N'-dibenzyl)diamino-1,16-S-thio-benzoyl-hexadeca-1,15-diene (TE16).

The precursors according to the invention are presented optionally in the form of salts. The hydrochlorides, the citrates, the tartrates, the maleates or the lactates can be mentioned as examples.

The invention also relates to the cyclized derivatives generated from the precursors of thiazolium described above.

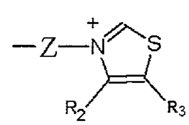
These derivatives correspond to general formula (VI)



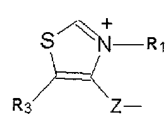
(VI)

in which

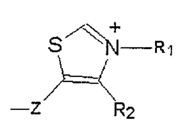
. R_b represents R_1 or T, T representing the group of formula



. R_d represents R_2 or P, P representing the group of formula



R_c represents R_3 or U, U representing the group of formula



R_1, R_2, R_3 and Z being as defined above,

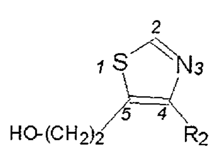
it being understood that $R_b = T$ if $R_c = R_3$ and $R_d = R_2$; $R_d = P$ if $R_c = R_3$ and $R_b = R_1$; and $R_c = U$ if $R_b = R_1$, and $R_d = R_2$.

In accordance with the invention, the precursors of thiazolium of general formula (III) to (IV) defined above can be obtained by a process characterized in that it comprises the reaction in basic medium of a thiazole derivative of formula (VI), as illustrated in the examples.

In an advantageous fashion, in order to obtain R_a = RCO–, a thiazolium derivative of formula (VI) is reacted with an RCOR' derivative, where R is as defined above and R' is a halogen atom, and in order to obtain R_a = RS– the said thiazolium derivatives of formula (VI) are reacted with a thiosulphate derivative RS_2O_3Na.

The N-duplicated series of thiazolium salts is obtained, generally speaking, by reacting a thiazole derivative suitably substituted with an alkyl dihalide under reflux in an organic solvent.

The duplicated C series on the C5 carbon of the thiazole ring, which comprises an oxygen in the Z chain, is obtained by reacting a thiazole derivative of general formula (VII)

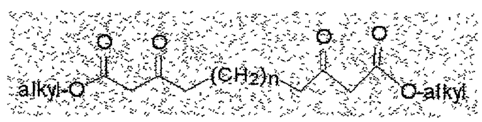


(VII)

with an alkane dihalide, in basic medium, then the addition of R_1X, the reaction medium being advantageously taken to reflux in an organic solvent, in particular alcohol such as ethanol, for a length of time sufficient to obtain the quaternization of the nitrogen atom of the thiazole by fixation of $\underline{R}_1$.

The opening of the obtained thiazolium ring is then carried out in basic medium, and by the action either of R-COCl, or of $R-S_2O_3Na$.

In order to obtain the C-duplicated series on the 5 carbon of the thiazole ring and not comprising oxygen in the <u>Z</u> chain, a compound of structure



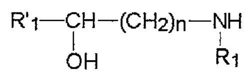
is firstly synthesized by reacting an alkyl acetoacetate with NaH, in an organic solvent, at a temperature of the order of 0°C, then the compound formed with for example an alkyllithium is alkylated and a dihalogenoalkane is added to the reaction medium.

The compound obtained is dibrominated by adding bromine at a temperature of the order of 0°C, then thioformamide is added and the reaction mixture is left under reflux for several days. By adding R_1X to the reaction mixture, then subjecting it to reflux for several days, a thiazolium is obtained the opening of which is then carried out in basic medium.

In order to obtain the C-duplicated series on the C4 carbon of the thiazole ring, and not comprising

oxygen in the Z chain, a $Z(CO\text{-}CH_2X)_2$ compound is reacted with $CH(=S)NH_2$, then R_1X is added.

The invention also relates to a process for obtaining haloalkylamines corresponding to general formula (II). This process is characterized by the alkylation of an aminoalcohol of formula



by an α, ω-dihalide of alkyl X-Z-X, which leads to a bis-aminoalcohol treated with a compound capable of releasing the W group.

The alkylation of the aminoalcohol is carried out for example with an alkyl α, ω- dichloride, of formula Cl-Z-Cl, in ethanol, in the presence of diisopropylethylamine, the aminoalcohol being in a large excess in relation to the halide (approximately 2.1/1). The bis-aminoalcohol obtained is then treated with a compound capable of releasing W, which can be for example thionyl chloride, in dichloromethane, in order to obtain a compound in which W represents Cl, or with the chloride of a sulphonic acid, for example tosyl chloride in order to obtain a compound in which W = $CH_3\text{-}C_6H_4\text{-}SO_3\text{-}$.

Study of the action of the products of the invention vis-à-vis parasites, and in particular *Plasmodium,* has shown that they have a strong action *in vitro.*

Thus, the values of IC_{50} (50% inhibitory concentration of the parasite) are of the order of nM vis-à-vis *P. falciparum.*

The invention therefore relates to the advantageous use of the properties of the precursors of the invention and of cyclized thiazolium compounds for the development of pharmaceutical compositions.

The pharmaceutical compositions of the invention are characterized in that they contain an effective quantity of at least one precursor as defined above, or of at least one cyclized compound of thiazolium, in combination with an inert pharmaceutical vehicle or at least one cyclized thiazolium compound.

The invention also relates to the use of at least one of the said precursors, or at least one of the said cyclised thiazolium compounds, to manufacture medicaments for the treatment of infectious diseases, in particular maleria or babesiosis in man or animals.

These compositions optionally contain the active ingredients of other medicaments. Their combination with other anti-malarial drugs (such as lysosomotropic agents, atovaquone, antifolic or antifolinic agents, or artemisinin or one of its derivatives) for reasons of pharmacological synergy or to avoid resistance can in particular be mentioned.

They can also be used to advantage in combination with compounds facilitating their assimilation.

The pharmaceutical compositions of the invention can be administered in different forms, more especially by oral or injectable route or also by rectal route.

For administration by oral route, tablets, pills, pressed tablets, gelatin capsules, drops can in particular be used.

Other forms of administration include solutions injectable by intravenous, sub-cutaneous or intramuscular route, developed from solutions which are sterile or can be sterilized. It can also concern suspensions or emulsions.

Suppositories can also be used for other forms of administration.

The compositions of the invention are particularly suitable for the treatment of infectious diseases in man and animals, in particular malaria or babesiosis.

By way of example, the dose which can be used in man corresponds to the following doses: therefore 0.02 to 80 mg/kg in one or more doses is for example administered to the patient.

The invention also relates to the biological reagents containing as active ingredients, the precursors of thiazolium defined above.

These reagents can be used as references or standards in studies of possible anti-parasitic action.

Other characteristics and advantages of the invention will become clear in the examples which follow relative to obtaining precursors of thiazolium and in the study of their anti-parasitic activity. In these examples, reference will be made to Figures 1 to 8, which represent respectively,

- Figure 1, the anti-malarial action of a precursor of thiazolium (designated by TE4c in the examples), and corresponding thiazolium (T4) as a function of the concentration of drug, according to the Desjardins test, (Desjardins R.E. et al, Antimicrob. Agents Chemother. 1979, 16, 710-718),

- Figures 2 and 3, the pharmacokinetics in the mouse of a precursor of thiazolium according to the invention at a low dose (designated by TE4c in the examples) after administration by ip and *per os* route,

- Figure 4, a semi-logarithmic representation of the pharmacokinetics in the mouse of precursors and of a drug according to the invention, after administration by ip and *per os* route,

- Figures 5A and 5B, the pharmacokinetics of a precursor and of a drug of the invention in the mouse after administration by ip and *per os* route,

- Figures 6 and 7, the pharmacokinetics in the mouse after administration by ip *per os* route, and

- Figures 8A and 8B, the pharmacokinetics of precursors of the invention in the monkey.

In the different diagrams given in the examples, the substituents have the meanings given above, X represents a counter ion,

Me = methyl, Et = ethyl, Ph or Φ = C_6H_5-,

DMSO=dimethylsulphoxide, THF= tetrahydrofuran, Bu = butyl.

I. SYNTHESIS OF THIAZOLIUM PRECURSORS

A. Synthesis of disulphide prodrugs (TS):

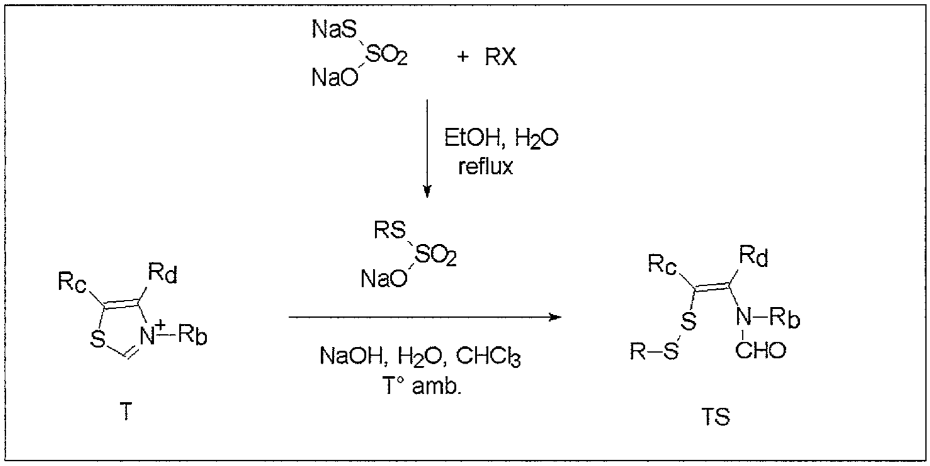


Diagram 1

General operating method:

a) Synthesis of the alkyl thiosulphate (Bunte salt)

30 mmoles of halogen derivative are dissolved in 15 mL of ethanol and 5g (30 mmol) of sodiumthiosulphate in a minimum amount of water are added. The mixture is heated to reflux for 5 days. The solution is evaporated to dryness and the crude residue obtained is used without purification.

b) Synthesis of the disulphide prodrug

2.6 mmoles of thiazolium drug are dissolved in 10 mL of water. 0.6g of NaOH then 10 mL of $CHCl_3$ are added and the mixture is stirred vigorously for 10 mn. 7.8 mmoles

of the alkyl thiosulphate obtained previously is then added dropwise and the mixture is stirred at ambient temperature for 2 hours. The organic phase is separated and washed with a 5% HCl solution. It is then neutralized with a solution of $NaHCO_3$, dried with Na_2SO_4 and concentrated. The oil obtained is purified on silica gel eluting with a CH_2Cl_2/MeOH mixture (9.5/0.5).

1. Synthesis of N,N'-diformyl-N,N'-di[1-methyl-2-tetrahydro-furfurylmethyldithio-4-hydroxybut-1-enyl]-1,12-diaminododecane (TS3a)

a) Preparation of tetrahydrofurfurylmethyl thiosulphate

The preparation is carried out according to §a of the general operating method above, starting from tetrahydrofurfuryl chloride.

NMR ^1H (250 MHz, D_2O): δ 4.04 (m,1H,CH_2-C*H*-O), 3.61(m,2H, -CH_2-O), 3.00(m,2H,S-CH_2-CH), 1.47-1.88(m,4H,-CH-CH_2-CH_2-)

b) Synthesis of TS3a

According to §b of the general operating method above, starting from T3 (see its preparation further on) and Bunte salt obtained previously, a yellowish oil is obtained.

NMR ^1H (250 MHz, $CDCl_3$): δ 7.88-7.99(2s,2H,C*H*O), 3.95(m,2H,O-C*H*-CH_2), 3.7(m,8H,-CH_2-OH+CH-OCH_2-CH_2), 3.32(m,4H,S-CH_2-), 2.8(m,8H,N-CH_2-+=C-CH_2), 1.64-1.94(m,18H,-N-CH_2-CH_2-+-CH-CH_2-CH_2-+CH_3-C=), 1.26(m,16H,(CH_2)$_8$).

2. Synthesis of N,N'-diformyl-N,N'-di[1-methyl-2-propyl-dithio-4-hydroxybut-1-enyl]-1,12-diaminododecane (TS3b)

a) Preparation of propyl thiosulphate

The preparation is carried out according to §a of the general operating method above, starting from propyl bromide.

NMR ^{1}H (250 MHz, D_2O): δ 0.74 (t, 2H, -CH_3), 1.51 (m, 2H, -$CH_2CH_2CH_3$), 2.86 (t, 2H, S-CH_2-CH_2-)

b) Preparation of TS3b

According to §b of the general operating method above, starting from T3 (see its preparation further on) and the Bunte salt obtained previously, a yellowish oil is obtained.

NMR ^{1}H (250 MHz, $CDCl_3$): δ 7.91-7.99(2s,2H,CHO), 3.8(m,4H,-CH_2-OH), 3.39(m,4H,S-CH_2-), 2.91(t,4H, =C-CH_2), 2.62(t,4H,N-CH_2-), 2.00(d,6H,CH_3-C=), 1.64(m,8H,-N-CH_2-CH_2-+-S-CH_2-CH_2-), 1.26(m,16H,-$(CH_2)_8$-), 0.97(t,6H,-S-CH_2-CH_2-CH_3).

3. Synthesis of N,N'-diformyl-N,N'-di[1-methyl-2-benzyl-dithio-4-hydroxybut-1-enyl]-1,12-diaminododecane (TS3c)

a) Preparation of benzyl thiosulphate

The preparation is carried out according to § a of the general operating method above, starting from benzyl bromide.

NMR ^{1}H (250 MHz, D_2O): δ 4.13(s,2H,-CH_2-), 7.23(m,5H,-ArH).

b) Preparation of TS3c

According to § b of the general operating method above, starting from T3 (see its preparation further on) and the Bunte salt obtained previously, a yellowish oil is obtained.

NMR ^1H (250 MHz, $CDCl_3$): δ 7.91-7.99(2s,2H,C*H*O), 3.89 (s,4H,S-CH_2-Ph), 3.73(t,4H,CH_2-OH), 3.40(t,4H,N-CH_2-), 2.75(t,4H,=C-CH_2), 1.96(s,6H,CH_3-C=), 1.52(m,4H,-N-CH_2-CH_2-), 1.25(m,16H,-(CH_2)$_8$-).

4 Synthesis of N,N'-diformyl-N,N'-di[1-methyl-2-(2-hydroxyethyl)dithio-4-hydroxybut-1-enyl]-1,12-diaminododecane (TS3d)

a) Preparation of 2-hydroxyethyl thiosulphate

The preparation is carried out according to §a of the general operating method above, starting from 2-chloroethanol.

NMR ^1H (250 MHz, D_2O): δ 3.32 (t,2H,S-CH_2), 3.98(t,2H,-CH_2-OH)

b) Preparation of TS3d

According to §b of the general operating method above, starting from T3 (see its preparation further on) and the Bunte salt obtained previously, an oil is obtained.

NMR ^1H (250 MHz, $CDCl_3$): δ 7.91-7.87 (2s,2H,C*H*O), 4.61(m,4H,-S-CH_2-CH_2-OH), 3.75(m,4H,=C-CH_2-CH_2-OH), 3.33(m,4H,S-CH_2-), 2.87(t,4H,=C-CH_2), 2.78(t,4H,N-CH_2-), 1.95(d,6H,CH_3-C=), 1.45(m,4H,-N-CH_2-CH_2-), 1.20(m,16H,-(CH_2)$_8$-).

5. Synthesis of N,N'-diformyl-N,N'-di[1-methyl-2-propyldithio-4-methoxybut-1-enyl]-1,12-

diaminododecane (TS4b)

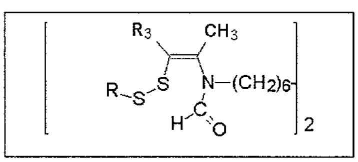
According to § b of the general operating method above, starting from T4 (see its preparation further on) and propyl thiosulphate, a yellowish oil is obtained.

NMR ^1H (250 MHz, $CDCl_3$): δ 7.91 and 7.99 (2s, 2H, CHO), 3.8 (m, 4H, $-CH_2$-OH), 3.39 (m, 4H, S-CH_2-), 2.91 (t, 4H, =C-CH_2), 2.62 (t, 4H, N-CH_2-), 2.00 (s, 6H, CH_3-C=), 1.64 (m, 9H, -N-CH_2-CH_2- + -S-CH_2-CH_2-), 1.26 (m, 16H, -$(CH_2)_8$-), 0.97 (t, 6H, -S-CH_2-CH_2-CH_3).

6. Synthesis of N,N'-diformyl-N,N'-di[1-methyl-2-propyldithio-ethenyl]-1,12-diaminododecane (TS6b)

According to § b of the general operating method above, starting from T6 (see its preparation further on) and of propyl thiosulphate, a yellowish oil is obtained.

NMR ^1H (250 MHz, $CDCl_3$): δ 8.02 (s, 2H, CHO), 6.03 (s, 2H, =C-H), 3.47 (t, 4H, N-CH_2-), 2.69 (t, 4H, S-CH_2-), 1.95 (s, 6H, CH_3-C=), 1.72 (m, 4H, -S-CH_2-CH_2-), 1.59 (m, 4H, -N-CH_2-CH_2-) , 1.26 (m, 16H, -$(CH_2)_8$-), 0.99 (t, 6H, -S-CH_2-CH_2-CH_3).



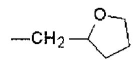
compounds	R_3	R	Yield %	IC_{50} (nM)
TS3a	$-CH_2-CH_2-OH$		60	1.0
TS3b	"	$-C_3H_7$	63	1.3
TS3c	"	$-CH_2-C_6H_5$	58	1.6
TS3d	"	$-CH_2-CH_2-OH$	30	2.2
TS4b	$-CH_2-CH_2-OCH_3$	$-C_3H_7$	60	3.5
TS6b	H	$-C_3H_7$	34	3.1

Table 1

B. Synthesis of thioester prodrugs (TE):

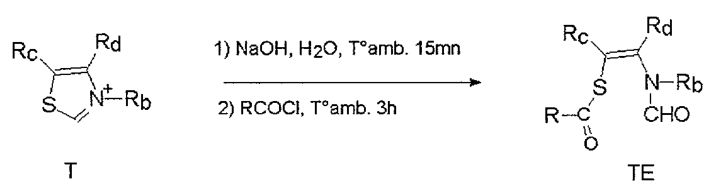


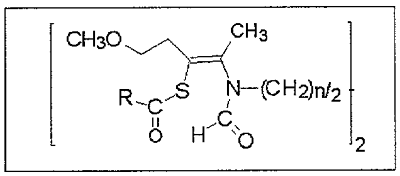
Diagram 2

General operating method:

3.15 mmoles of thiazolium salt are suspended in 10 mL of water and 0.75g (6 equivalents) of NaOH are added. The solution obtained is left under magnetic stirring for 15 min. Then, 9.6 mmoles (3 equivalents) of acid chloride in solution in 20 mL of $CHCl_3$ are added dropwise and the reaction mixture is stirred at ambient temperature for 3 hours. The organic phase is separated, washed with water saturated with NaCl then dried over $MgSO_4$ and

concentrated in an evaporator. The residue obtained is purified on silica gel (eluent CH_2Cl_2/MeOH: 95/5).

1. Synthesis of thioester derivatives of the N duplicated series (compounds TE4a-j, TE3 and TE8):



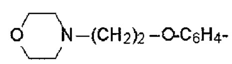
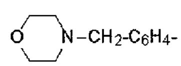
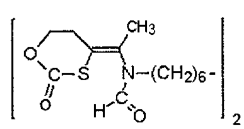
compounds	R	n	Yield %	IC_{50} (nM)
TE4a	Me-	12	69	14
TE4b	t-Bu-	12	72	12
TE4c	C_6H_5-	12	70	2.0
TE4d	*4*-(MeO) C_6H_4-	12	65	3.4
TE4e		12	84	6.4
TE4f	*4*-(Et_2N-CH_2)-C_6H_4-	12	71	2.3
TE4g		12	80	2.3
TE4j	*4*-(MeOCO)- C_6H_4-	12	76	2.7
TE8	C_6H_5-	16	70	1.6
TE3			20	3

Table 2

1.1. Synthesis of N,N'-diformyl-N,N'-di[1-methyl-2-S-thiobenzoyl-4-methoxybut-1-enyl]-1,12-diaminododecane (TE4c)

According to the operating method described above, starting from T4 and using benzoyl chloride, a white powder is obtained (Yield = 70%)

NMR ^{1}H (250 MHz, $CDCl_3$): δ 7.90-7.36 (m, 12H, C*H*O + Ar*H*), 3.52-3.29 (m, 8H, CH_3OCH_2-, N-CH_2-), 3.30 (s, 6H, CH_3O), 2.75 (t, 4H, $CH_3OCH_2CH_2$-), 2.06 (s, 6H, CH_3-C=), 1.57-1.09 (m, 20H, -$(CH_2)_{10}$-).

MS ES^+: m/e 725 ($[M+H]^+$, 100).

1.2. Synthesis of N,N'-diformyl-N,N'-di[1-methyl-2-S-(p-diethylaminomethylphenylcarboxy)-thio-4-methoxybut-1-enyl]-1,12-diaminododecane (TE4f)

a) Synthesis of α-diethylamino-paratoluic acid

1 g (1 equivalent) of α-chloroparatoluic acid and 1.22 mL (2 equivalents) of diethylamine are placed in solution in 30 mL of acetonitrile. The reaction mixture is taken to reflux for 48 hours. The solvent is evaporated off under vacuum and the residue is purified by chromatography on silica gel column (CH_2Cl_2/MeOH 60/40 then pure MeOH). The product is obtained in the form of a white powder after precipitation from hexane. (Yield = 63%).

NMR ^{1}H (250 MHz, $DMSOD_6$): δ 7.84 and 7.29 (2d, 2x2H, Ar*H*), 3.50 (s, 2H, N-CH_2-Ar), 2.40 (q, 4H, $N(CH_2-CH_3)_2$), 0.9 (t, 6H, $N(CH_2-CH_3)_2$).

MS ES^+: m/e 208 ($[M+H]^+$, 100).

b) Synthesis of α-diethylaminoparatoluic acid chloride

0.3 g (1.45 mmol) of α-diethylaminoparatoluic acid are placed in 10 mL of $CHCl_3$ and 0.32 mL of $SOCl_2$ are added. The solution is taken to reflux for 12 hours The solvent is evaporated off under vacuum and the residue is recrystallized from ethyl ether. 323 mg of product is obtained, in the form of its hydrochloride (Yield = 85%). MS ES^+: m/e 226 ($[M+H]^+$, 100), 228 ($[M+H]^+$, 30).

c) Synthesis of TE4f (in the form of the hydrochloride)

0.7 g (0.95 mmol) of T4 are suspended in 10 mL of water and 0.23 g (5.71 mmol) of NaOH are added. The solution obtained is left under stirring for 15 min. Then, 0.75 g (2.86 mmol) of α-diethylaminoparatoluic acid chloride in solution in 20 mL of $CHCl_3$ and 0.4 mL (2.86 mmol) of triethylamine are added dropwise. The reaction mixture is stirred at ambient temperature for 4 hours The organic phase is separated, washed with water and dried over $MgSO_4$ and concentrated with a rotary evaporator. The oil obtained is purified by chromatography on silica gel column (CH_2Cl_2/MeOH 95/5 then pure MeOH). The hydrochloride is obtained by bubbling gaseous HCl through a solution of the base in ether at 0°C for 3 hours This salt is obtained in the form of a foamy precipitate. (Yield = 54%).

NMR ^1H of the free base: (250 MHz, $CDCl_3$): δ 8.00-7.48 (m, 10H, C*H*O+ Ar*H*), 3.62-3.37 (m, 12H, CH_3OCH_2-CH_2-+ N-CH_2-Ar), 3.35 (s, 6H, CH_3O), 2.80 (t, 4H, N-CH_2-), 2.50 (q,

8H, $N(CH_2-CH_3)_2$), 2.15 (s, 6H, $CH_3-C=$), 1.50-1.12 (m, 20H, $-(CH_2)_{10}-$), 1.08 (t, 12H, $N(CH_2-CH_3)_2$).
MS ES^+: m/e 448.5 ($[M+2H]^+$, 100).

1.3. Synthesis of N,N′-diformyl-N,N′-di[1-methyl-2-S-(p-morpholino-methylphenylcarboxy)-thio-4-methoxybut-1-enyl]-1,12-diaminododecane (TE4g)

a) Synthesis of α-morpholinoparatoluic acid

4.04 g (1 equivalent) of α-chloroparatoluic acid and 4.13 g (2 equivalents) of morpholine are placed in solution in 150 mL of toluene. The reaction mixture is taken to reflux for 24 hours The morpholine hydrochloride is eliminated by warm filtration through a Buchner. The product crystallizes from the filtrate at ambient temperature. After filtration and drying, 3.63 g of product is obtained in the form of a white powder (Yield = 70%).
NMR ^1H (250 MHz, $DMSOD_6$): δ 7.84 and 7.37 (2d, 2x2H, ArH), 3.53 (t, 4H, CH_2OCH_2), 3.48 (s, 2H, $Ar-CH_2-$), 2.31 (t, 4H, CH_2-N-CH_2-).
MS ES^+: m/e 222 ($[M+H]^+$, 100).

b) Synthesis of α-morpholinoparatoluic acid chloride

2.33 g of α-morpholinoparatoluic acid are placed in 30 mL of CH_2Cl_2 and 3.76 g of $SOCl_2$ are added. The not very homogenous solution is taken to reflux for 48 hours The white precipitate obtained is filtered, washed with

CH_2Cl_2 and dried. 2.65 g of product is obtained (Yield = 70%).

NMR ^1H (250 MHz, $DMSOD_6$): δ 7.97 and 7.78 (2d, 2x2H, Ar*H*), 4.40 (s, 2H, Ar-CH_2-), 3.86 (m, 4H, CH_2OCH_2-), 3.18 (m, 4H, CH_2-N-CH_2-).

MS ES^+: m/e 240 ($[M+H]^+$, 100), 242 ($[M+H]^+$, 30).

c) Synthesis of TE4g (in the form of the TE4go dioxalate or TE4gt ditartrate salt)

1.08 g of T4 are suspended in 10 mL of water and 0.37 g (6 equivalents) of NaOH are added. The solution obtained is left under stirring for 15 min. Then, 1.15 g (3 equivalents) of the hydrochloride of α-morpholinoparatoluic acid chloride in solution in 20 mL of $CHCl_3$ and 0.42 g of triethylamine are added dropwise. The reaction mixture is stirred at ambient temperature for 3 hours The organic phase is extracted then dried over $MgSO_4$ and concentrated with a rotary evaporator. The residue obtained is taken up in ether and water. The organic phase is extracted, washed twice with water then dried over $MgSO_4$ and concentrated. The oil obtained is taken up in a minimum amount of ether and an ethereal solution containing 0.41 g of oxalic acid is added. A white precipitate forms immediately (TE4go: Yield = 80%). A other sample of oil (7.7 g)is placed in solution with an aqueous solution (1N) containing 2 equivalents of tartaric acid (+). The solution is evaporated to dryness. The residue is dissolved in ethanol, the solution is again evaporated. A solid foam (TE4gt, Pf: 82-85°C) is obtained.

Characterization of the free base:

NMR ^{1}H (250 MHz, $CDCl_3$): δ 7.90-7.36 (m, 10H, C*H*O + Ar*H*), 3.69 (t, 8H, CH_2OCH_2-), 3.52-3.32 (m, 12H, $CH_3OCH_2CH_2$- + N-CH_2-Ar), 3.30 (s, 6H, CH_3O), 2.77 (t, 4H, N-CH_2-), 2.42 (t, 8H, -CH_2-N-CH_2-), 2.09 (s, 6H, CH_3-C=), 1.57-1.09 (m, 20H, -$(CH_2)_{10}$-).
MS ES^+: m/e 462 ($[M+2H]^+$, 100), m/e 923 ($[M+H]^+$, 10).

1.4. Synthesis of N,N'-diformyl-N,N'-di[1-methyl-2-S-(p-phthaloyl)-thio-4-methoxybut-1-enyl]-1,12-diaminododecane (TE4j)

According to the operating method described above, starting from T4 and using p-methoxycarbonylbenzoyl chloride, a white powder is obtained (Yield = 76%).
NMR ^{1}H (250 MHz, $CDCl_3$): δ 7.90-7.36 (m, 10H, C*H*O + Ar*H*), 3.97 (s, 6H, CH_3OCO), 3.57-3.35 (m, 8H, $CH_3OCH_2CH_2$-), 3.30 (s, 6H, CH_3O), 2.82 (t, 4H, N-CH_2-), 2.13 (s, 6H, CH_3-C=), 1.58-1.17 (m, 20H, -$(CH_2)_{10}$-).
MS ES^+: m/e 421 ($[M+2H]^{++}$, 20). 841 ($[M+H]^+$, 100).

1.5. Synthesis of N,N'-diformyl-N,N'-di[1-methyl-2-S-thiobenzoyl-4-methoxybut-1-enyl]-1,16-diaminohexadecane (TE8)

According to the general operating method described above, starting from 1,16-hexadecamethylene bis [4-methyl-5-(2-methoxyethyl) thiazolium] diiodide, T8, and using benzoyl chloride, a yellowish oil is obtained (Yield = 72%).

NMR ^1H (250 MHz, $CDCl_3$): δ 7.90-7.36 (m, 12H, C*H*O + Ar*H*), 3.50-3.32 (m, 8H, CH_3OCH_2-, N-CH_2), 3.30 (s, 6H, CH_3O), 2.75 (t, 4H, $CH_3OCH_2CH_2$-), 2.06 (s, 6H, CH_3-C=), 1.57-1.09 (m, 28H, -$(CH_2)_{10}$-).
MS ES^+: m/e 781 ($[M+H]^+$, 100).

1.6 Synthesis of N,N'-diformyl-N,N'-di[1(2-oxo-4,5-dihydro-1,3-oxathian-4-ylidene)ethyl] 1,12-diaminododecane (TE3)

2.8 mmoles (2 g) of thiazolium salt T3 [1,12-dodecamethylene bis [4-methyl-5-(2-hydroxyethyl) thiazolium dibromide] are dissolved in 4.4 mL of ethanol and 12.2 mmol (4.5 mL, 4 equivalents) of NaOH (10%) are added. The solution obtained is left under magnetic stirring for 15 min. Then, 6 mL (1.12 g, 2 equivalents) of 4-nitrophenylchloroformate in solution in ethyl acetate are added dropwise and the reaction mixture is stirred at ambient temperature for 2 hours. Ethyl acetate is added. The organic phase is washed successively with water, a saturated solution of sodium hydrogen carbonate, water, then dried over $MgSO_4$ and concentrated in an evaporator. The yellow oil obtained is purified over silica gel (eluent CH_2Cl_2, then adding 1% MeOH, then 2%). Yield: 20%.

NMR ^1H (250 MHz, $CDCl_3$): δ 8.2 and 7.88 (2s,2H,C*H*O); 4.43-4.40(t,4H,-CH_2OCO-); 3.33-3.27(t,N-CH_2); 2.79-2.77 (t,4H,CH_2-CH_2=); 1.88(s,6H,CH_3; 1.46-1.13(m,20H,$(CH_2)_{10}$).
MS ES^+: m/e 541 ($[M+H]^+$, 100).

2. Synthesis of thioesters of the C duplicated series

2.1. C5 duplicated compounds comprising an O in the alkyl chain (TE9 and TE10):

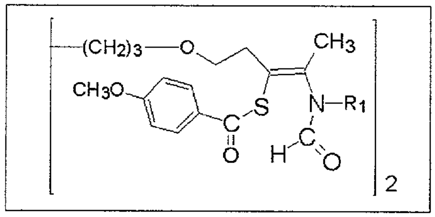
These prodrugs are synthesized according to the general operating method described previously (Diagram 2).

Starting from 3,10-dioxadodecamethylenebis[5-(1,4-dimethyl)thiazolium] diiodide, T9, and p-methoxybenzoyl chloride, 2,17-(N,N'-diformyl-N,N'-dimethyl)diamino-3,16-S-thio-p-methoxybenzoyl-6,13-dioxaoctadeca-2,16-diene, TE9 is obtained, in the form of a colourless oil. Yield: 65 %.

NMR ^1H (200 MHz, $CDCl_3$): δ 7.93-6.87 (m, 10H, C*H*O + Ar*H*), 3.58(s,6H,$2CH_3$), 3.55(t,4H,$2CH_2$), 3.37(t,4H,$2CH_2$), 2.89(s,6H,$2CH_3$), 2.77(t,4H,$2CH_2$), 2.03(s,6H,$2CH_3$), 1.52-1.30(m,8H,$4CH_2$).

Starting from 3,10-dioxadodecamethylenebis[5-(1-benzyl,4-methyl)-thiazolium] dibromide, T10, and p-methoxybenzoyl chloride, 2,17- (N,N'-diformyl-N,N'-dibenzyl)diamino-3,16-S-thio-p-methoxybenzoyl-6,13-dioxaoctadeca-2,16-diene, TE10, is obtained in the form of a colourless oil. Yield: 70 %.

NMR ^1H (200 MHz, $CDCl_3$): δ 8.06-6.92 (m, 20H, C*H*O + Ar*H*), 4.68 (s, 4H, 2 CH_2), 3.91 (s, 6H, 2 CH_3), 3.50 (t, 4H, $2CH_2$), 3.38 (t, 4H, $2CH_2$), 2.75 (t, 4H, $2CH_2$), 2.07 (s, 6H, $2CH_3$), 1.56-1.31 (m, 8H, $4CH_2$).



compounds	R_1	IC_{50} (nM)
TE9	CH_3	260
TE10	C_6H_5-CH_2	12

Table 3

2.2. C5 duplicated compounds not comprising O in the alkyl chain (TE12 and TE13):

These prodrugs are synthesized according to the general operating method described previously (Diagram 2).

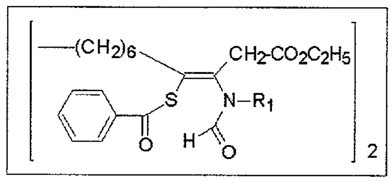
Starting from dodecamethylenebis[5-(1-methyl-4-ethoxycarbonylethyl)-thiazolium] diiodide, T12, ethyl 3,18- (N,N'-diformyl-N,N'-dimethyl)diamino-4,17-S-thiobenzoyleicosa-3,17-dienedioate, TE12, is obtained. Colourless oil. Yield 70%.

NMR ^1H (200 MHz, $CDCl_3$): δ 7.94-7.39 (m, 12H, C*H*O + Ar*H*), 4.14 (q, 4H, 2 OCH_2-), 3.45 (s, 4H, 2 CH_2), 2.88 (s, 6H, 2 CH_3), 2.44 (t, 4H, 2CH_2), 1.27-1.19 (m, 26H, -$(CH_2)_{10}$+ 2 CH_3).

Starting from dodecamethylenebis[5-(1-benzyl-4-ethoxycarbonylethyl)-thiazolium] dibromide, T13, ethyl 3,18-(N,N'-diformyl-N,N'-dibenzyl)diamino-4,17-S-thiobenzoyleicosa-3,17-dienedioate, TE13, is obtained.

Colourless oil. Yield 64%.

NMR ^1H (200 MHz, $CDCl_3$): δ 8.24-7.26 (m, 22H, C*H*O + Ar*H*), 4.70 (s, 4H, 2CH_2-Ar), 4.23 (q, 4H, 2OCH_2-), 3.44 (s, 4H, 2CH_2), 2.51 (t, 4H, 2CH_2), 1.52-1.29 (m, 26H,-$(CH_2)_{10}$+ 2CH_3).



compounds	R_1	CI_{50} (nM)
TE12	CH_3-	16
TE13	C_6H_5-CH_2-	650

Table 4

2.3. C4 duplicated Compounds not comprising O in the alkyl chain.

These prodrugs are synthesized according to the general operating method described previously (Diagram 2).

Starting from dodecamethylenebis[4-(1-methyl)-thiazolium] di-iodide, T15, 2,15-(N,N'-diformyl-N,N'-dimethyl)diamino-1,16-S-thiobenzoyl-hexadeca-1,15-diene, TE15, is obtained.

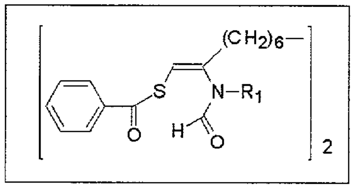
Colourless oil. Yield 70%.

NMR ^1H (200 MHz, $CDCl_3$): δ 7.94-7.39 (m, 12H, C*H*O + Ar*H*), 5.7 (2H, =C*H*), 2.88 (s, 6H, 2 N-CH_3), 2.48 (t, 4H, 2 =C-CH_2), 1.27-1.19 (m, 20H,-$(CH_2)_{10}$).

Starting from dodecamethylenebis[4-(1-benzyl)-thiazolium] dibromide, T16, 2,15-(N,N'-diformyl-N,N'-dibenzyl)diamino-1,16-S-thiobenzoyl-hexadeca-1,15-diene, TE16, is obtained.

Colourless oil. Yield 64%.

NMR ^1H (200 MHz, $CDCl_3$): δ 8.24-7.56 (m, 22H, C*H*O + Ar*H*), 5.7 (2H, =C*H*), 4.37 (s, 4H, 2CH_2-Ar), 2.51 (t, 4H, 2 =C-CH_2), 1.52-1.29 (m, 20H).



compounds	R_1	IC_{50} (nM)
TE15	CH_3-	7 nM
TE16	C_6H_5-CH_2-	12 nM

Table 5

II. SYNTHESIS OF THIAZOLIUM SALTS

A. Synthesis of the compounds of the N duplicated series (compounds T3, T4, T6 and T8):

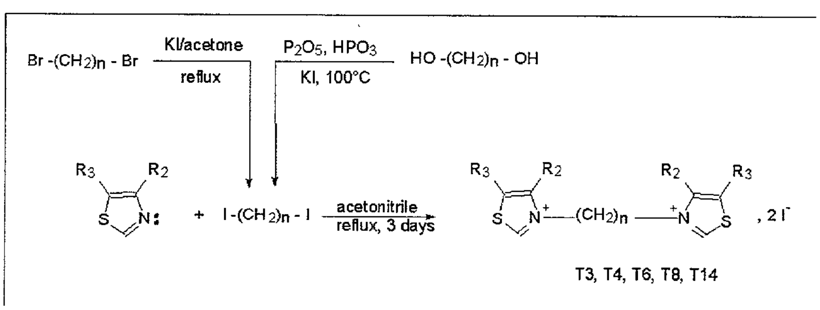


Diagram 3

General operating method for the synthesis of dihalides of α,ω-polymethylene bis thiazolium:

Appropriately substituted thiazole (11.5 mmol) is dissolved in 30 mL of acetonitrile. 3.8 mmol of alkyl diiodide (or dibromide) are added and the reaction mixture is taken to reflux for 3 days. The solution is concentrated with a rotary evaporator and the oily residue obtained is taken up in water and ether. The aqueous phase is washed with ether then concentrated under reduced pressure. The product is then crystallized from isopropanol.

1,12-diiodododecane is synthesized as follows: 10.22g (1 equivalent) of 1,12-dibromododecane is mixed with 14.26g (3 equivalents) of sodium iodide in 150 mL of acetone. After stirring for 15 minutes at ambient temperature, the solution is heated under reflux for 3 hours.

The acetone is then evaporated off with the rotary evaporator, the residue is taken up in ethyl ether and water and the product is extracted three times with ether. The ethereal phases are combined and are dried over magnesium sulphate. The white solid obtained is then recrystallized from methanol (M.p. 42-43°C). Yield= 95%.

1,16-diiodohexadecane is obtained from hexadecane-1,16-diol, by adding 5 g of this diol and 19 g of potassium iodide to a solution of 2.5 g of phosphoric anhydride and 5.2 mL of 85% phosphoric acid. The mixture is heated at 100°C for 5 hours. A dense oil forms, and the mixture is poured into 50 mL of water. The organic phase is separated, and the aqueous phase extracted with ether. The organic phases are discoloured by stirring with 50 mL of a 10% solution of sodium thiosulphate. The

ether is evaporated off. The oil obtained is crystallized from methanol (M.p. = 52°C). Yield: 82%.

1- Synthesis of 1,12- dodecamethylene bis [4-methyl-5-(2-hydroxyethyl) thiazolium] dibromide (T3)

According to the operating method described above, a hygroscopic white powder is obtained starting from 4-methyl-5-[2-hydroxyethyl] thiazole and 1,12-dibromododecane (Yield = 75%)

NMR ^1H (250 MHz, DMSO D_6): δ 10.08 (s, 2H, S-C*H*=), 4.45 (t, 4H, $^+N-CH_2-$), 3.62 (t, 4H, $HOCH_2CH_2-$), 3.02 (t, 4H, $HOCH_2CH_2-$), 2.50 (s, 6H, $CH_3-C=$), 1.77 (m, 4H, $^+N-CH_2CH_2-$), 1.60-1.25 (m, 16H, $-(CH_2)_8-$).

MS ES^+: m/e 227 (M^{++}, 100), m/e 533-535 ($M^{++}Br^-$, 10)

2- Synthesis of 1,12-dodecamethylene bis[4-methyl-5-(2-methoxyethyl)thiazolium] diiodide (T4)

According to the general operating method described above, a hygroscopic white powder is obtained starting from 4-methyl-5-(2-methoxyethyl) thiazole and 1,12-diiodododecane (Yield = 70%)

NMR ^1H (250 MHz, $CDCl_3$): δ 10.92 (s, 2H, S-C*H*=), 4.66 (t, 4H, $^+N-CH_2-$), 3.60 (t, 4H, $CH_3OCH_2CH_2-$), 3.35 (s, 6H, CH_3O), 3.07 (t, 4H, $CH_3OCH_2CH_2-$), 2.52 (s, 6H, $CH_3-C=$), 1.92 (m, 4H, $^+N-CH_2CH_2-$), 1.57-1.25 (m, 16H, $-(CH_2)_8-$).

MS ES^+: m/e 241 (M^{++}, 100), m/e 609 ($M^{++}I^-$, 5)

4-methyl-5-[2-methoxyethyl] thiazole is synthesized according to the process below:

10.20 mL of 4-methyl-5-[2-hydroxyethyl] thiazole is dissolved in 180 mL of anhydrous DMSO and 19 g of powdered potash are added. After stirring for 5 minutes, 5.30 mL of methyl iodide is introduced. The reaction mixture is stirred for 30 minutes at ambient temperature

under an inert atmosphere. On completion of the reaction (monitored by TLC), the mixture is poured into 100 mL of water followed by extraction 3 times with ether. The organic phase is then washed with water, then with water saturated in NaCl and finally, dried over sodium sulphate. The product obtained is purified on silica gel eluting with an AcOEt/hexane mixture (1/3). A yellow oil is obtained (Yield = 60%)

NMR ^1H (250 MHz, $CDCl_3$): δ 2.39 (s, 3H, $C\mathit{H}_3C$=), 3.00 (t, 2H, -$C\mathit{H}_2C$=), 3.36 (s, 3H, $C\mathit{H}_3O$), 3.55 (t, 2H, O-$C\mathit{H}_2$-),8.56 (s, 1H, S-CH=).

3- Synthesis of 1,12-dodecamethylenebis(4-methylthiazolium) diiodide (T6)

According to the general operating method described above, a white powder is obtained starting from 4-methylthiazole and 1,12-diiodododecane (Yield = 50%)

NMR ^1H (250 MHz, DMSO D6): δ 10.11 (s, 2H, S-CH=), 8.02 (s, 2H, S-CH=), 4.42 (t, 4H, $^+$N-$C\mathit{H}_2$-), 2.55 (s, 6H, $C\mathit{H}_3$-C=), 1.80 (m, 4H, $^+$N-$CH_2C\mathit{H}_2$-), 1.25 (m, 16H, -$(C\mathit{H}_2)_8$-).

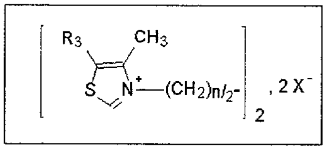
MS ES^+: m/e 183 (M^{++}, 100), m/e 493 ($M^{++}I^-$, 5)

4- Synthesis of 1,16-hexadecamethylenebis[4-methyl-5-(2-methoxyethyl)thiazolium] diiodide (T8)

According to the general operating method described above, a white powder is obtained starting from 4-methyl-5-[2-methoxyethyl] thiazole and 1,16-diiodohexadecane (Yield = 80%). M.p.: 210°C.

NMR ^1H (250 MHz, $CDCl_3$): δ 10.92 (s, 2H, S-CH=), 4.66 (t, 4H, $^+$N-$C\mathit{H}_2$-), 3.60 (t, 4H, $CH_3OC\mathit{H}_2CH_2$-), 3.35 (s, 6H, $C\mathit{H}_3O$), 3.07 (t, 4H, $CH_3OCH_2C\mathit{H}_2$-), 2.52 (s, 6H, $C\mathit{H}_3$-C=), 1.92 (m, 4H, $^+$N-$CH_2C\mathit{H}_2$-), 1.57-1.25 (m, 24H, -$(C\mathit{H}_2)_8$-).

MS ES^+: m/e 269 (M^{++}, 100), m/e 665 ($M^{++}I^-$, 10)



compounds	R_3	n	X	IC_{50} (nM)
T3	$-CH_2-CH_2-OH$	12	Br	2.25
T4	$-CH_2-CH_2-OCH_3$	"	"	0.65
T6	H	"	I	3
T8	$-CH_2-CH_2-OCH_3$	16	"	1.1

Table 6

B. Synthesis of compounds of the C duplicated series (T9, T10, T12 and T13):

1- Synthesis of the compounds duplicated on the C5 carbon of the thiazole ring.

1-1- Synthesis of the compounds comprizing an O in the alkyl chain (T9, T10):

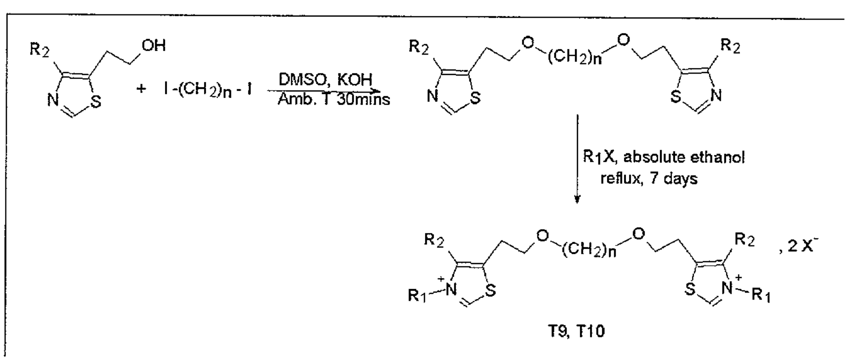


Diagram 4

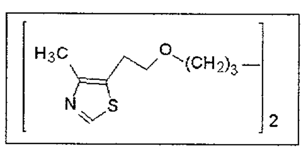
General operating method for the synthesis of the diiodides of 3,10-dioxadodecamethylenebis[5-(1-alkyl-4-methyl)thiazolium]: T9, T10) (Diagram 4).

1st stage: Dissolve 4-methyl-5-hydroxyethylthiazole (20.9 mmol) in anhydrous DMSO (50 ml). Add potassium hydroxide (83.6 mmol) and stir for 10 minutes. Add the diiodinated derivative (6.9 mmol) and stir at ambient temperature for 30 minutes. Add water and extract 3 times with ether. Wash the ethereal phase with water, then dry it over sodium sulphate. Purify by chromatography on silica gel eluting with AcOEt-Hexane (1-3).

2nd stage: Alkylation of bis-thiazole: Dissolve bis-thiazole (1 mmol) in absolute ethanol (40 ml). Add the desired halogenated derivative (2 mmol) and heat the mixture under reflux for approximately one week. Evaporate the ethanol and recrystallise from an iPrOH-$(iPr)_2O$ mixture.

a) Synthesis of 1,6-bis[2-(4-methylthiazol-5-yl)ethoxyhexane:

According to the general operating method (1st stage) described above, a colourless oil is obtained starting from 4-methyl-5-hydroxyethylthiazole and 1,6-diiodohexane (Yield = 60%)



NMR ^1H (200 MHz, $CDCl_3$): d 8.51 (s, 2H, CH), 3.54 (t, 4H, $-CH_2-$), 3.39 (t, 4H, $-CH_2$), 2.96 (t, 4H, $-CH_2-$), 2.32 (s, 6H, CH_3), 1.57-1.28 (m, 8H, $-CH_2-CH_2-$).

b) Synthesis of 3,10-dioxadodecamethylenebis[5-(1,4-dimethyl)thiazolium] diiodide (T9)

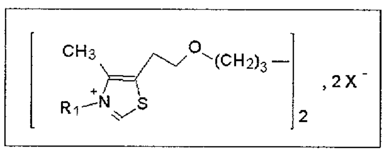
According to the general operating method (2nd stage) described above, a hygroscopic white solid is obtained starting from the product previously obtained and methyl iodide (Yield = 60%)

NMR ^1H (200 MHz, $CDCl_3$): d 10.99 (s, 2H, S-C*H*=), 4.33 (s, 6H, $2N^+CH_3$), 3.71 (t, 4H, $2CH_2$-O), 3.52 (t, 4H, 2O-CH_2), 3.03 (t, 4H, $2CH_2$), 2.51 (s, 6H, 2 =C-CH_3), 1.65-1.47 (m, 8H, 4-CH_2-).

c) Synthesis of 3,10-dioxadodecamethylenebis[5-(1-benzyl,4-methyl)-thiazolium] dibromide (T10)

According to the general operating method (2nd stage) described above, a hygroscopic white solid is obtained starting from the product obtained in the 1st stage and benzyl bromide (Yield = 74%)

NMR ^1H (200 MHz, $CDCl_3$): d 11.45 (s, 2H, S-C*H*=), 7.36-7.28 (m, 10H, 2Ar*H*), 3.65 (t, 4H, $2CH_2$-O), 3.44 (t, 4H, 2O-CH_2), 3.03 (t, 4H, $2CH_2$), 2.51 (s, 6H, 2 =C-CH_3), 1.57-1.34 (m, 8H, 4-CH_2-).



compounds	R_1	X	IC_{50} (nM)
T9	CH_3-	I	70
T10	C_6H_5-CH_2-	Br	2.5

Table 7

1-2- Compounds not comprizing an O in the alkyl chain (T12, T13)

This synthesis is carried out in 4 stages according to Diagram 5.

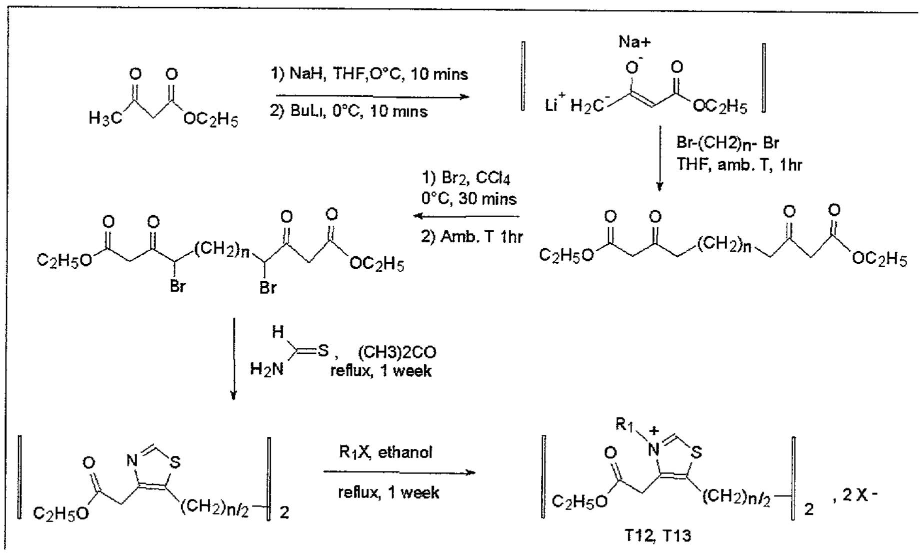
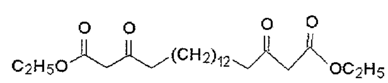


Diagram 5

a) Synthesis of ethyl 3,18-dioxoeicosanedioate:



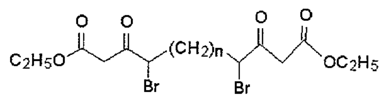
In a two-necked flask under argon, NaH (43.7 mmol) is put into suspension in anhydrous THF (100 ml). The reaction medium is cooled down in an ice bath and acetoethyl acetate is added dropwise (39.7 mmol). After stirring for 10 minutes at 0°C n-BuLi is added dropwise (1.56 M; 43.7 mmol). Stirring is carried out for a further 10 minutes at ambient temperature before proceeding with alkylation.

Dibromododecane (15.9 mmol) in solution in 20 ml of anhydrous THF is added dropwise to the previous solution. The reaction medium is allowed to return to ambient temperature and stirring is continued for 1 hour. Water

is added followed by extraction with ether (3 times). The organic phase is washed with a saturated NaCl solution, dried over sodium sulphate, filtered and evaporated to dryness. The product is purified by chromatography on silica gel eluting with AcOEt-Hexane (1-1). A white solid is obtained (Yield = 65 %); M.p. = 60°C.

NMR ^{1}H (200 MHz, $CDCl_3$): d 4.16 (q, 4H, $2CH_2$), 3.41 (s, 4H, $2CH_2$), 2.50 (t, 4H, $2CH_2$), 1.56-121 (m, 30H).

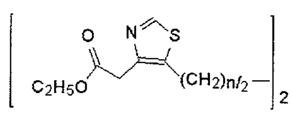
b) Synthesis of ethyl 4,17-dibromo-3,18-dioxoeicosanedioate:



The previous compound (3.8 mmol) is dissolved in 20 ml of CCl_4. The solution is cooled down to 0°C, and bromine is added dropwise (76 mmol), stirring is maintained at the same temperature for 30 minutes, then at ambient temperature for 1 hour. The solvent is evaporated off. The residue is dissolved in water, followed by extraction with ethyl acetate. The organic phase is dried over sodium sulphate, filtered and evaporated to dryness. Chromatography is carried out on silica gel eluting with AcOEt-Hexane (1-1). A yellowish oil is obtained (Yield = 64 %).

NMR ^{1}H (200 MHz, $CDCl_3$): d 4.42 (m, 6H, $2CH_2$+CH), 3.78-3.48 (m, 4H, $2CH_2$), 1.94-1.14 (m, 30H).

c) Synthesis of dodecamethylenebis[5-(4-ethoxycarbony-lethyl)thiazole]:



Thioformamide (23.4 mmol) in solution in 5 ml of acetone is added to a solution of 11.7 mmol of ethyl bis-

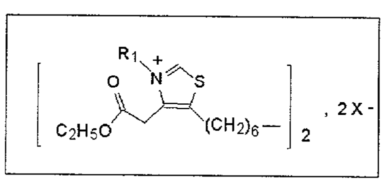
bromoacetoacetate in 5 ml of acetone and the reaction medium is stirred at 40°C for one week. The solvent is evaporated off and the residue is dissolved in water. The solution is extracted with AcOEt. Purification is carried out by chromatography (AcOEt-Hex: 1/1). A white solid is obtained (Yield = 50 %); M.p. = 112-114°C.
NMR ^{1}H (200 MHz, $CDCl_3$): d 8.54 (s, 2H, 2CH), 4.17 (q, 4H, $2CH_2$), 3.72 (s, 4H, $2CH_2$), 2.72 (t, 4H, $2CH_2$), 1.56-121 (m, 30H)

d) Alkylation of dodecamethylenebis[5-(4-ethoxycarbonyl ethyl)thiazole]:

The previous compound leads by alkylation on the nitrogen atom (according to the usual process described for T3 or T4) either to T12 using iodomethane, or to T13 using benzyl bromide.

Dodecamethylenebis[5-(1-methyl-4-ethoxycarbonylethyl)-thiazolium] diiodide (T12):
Yellow solid M.p. = 112°C; Yield = 55 %
NMR ^{1}H (200 MHz, $CDCl_3$): d 10.91 (d, 2H, 2CH), 4.42 (6H, N-CH_3), 4.25-4.16 (m, 8H, $2CH_2$+$2CH_2$), 2.91 (m, 4H, $2CH_2$), 1.62-1.26 (m, 26H).

Dodecamethylenebis[5-(1-methyl-4-ethoxycarbonylethyl)-thiazolium] dibromide (T13):
Yellow oil; Yield = 50 %
NMR ^{1}H (200 MHz, $CDCl_3$): d 11.26 (d, 2H, 2CH), 7.36-7.26 (m, 10H, ArH), 6.07(s, 4H, $2CH_2$), 4.02-3.92 (m, 12H, $6CH_2$), 2.91 (m, 4H, $2CH_2$), 1.62-1.26 (m, 26H).



compounds	R_1	X	IC_{50} (nM)

T12	CH_3-	I	13
T13	C_6H_5-CH_2-	Br	250

Table 8

2- Synthesis of compounds duplicated on the C4 carbon of the thiazole ring (T15 and T16).

This synthesis is carried out in 5 stages according to Diagram 6.

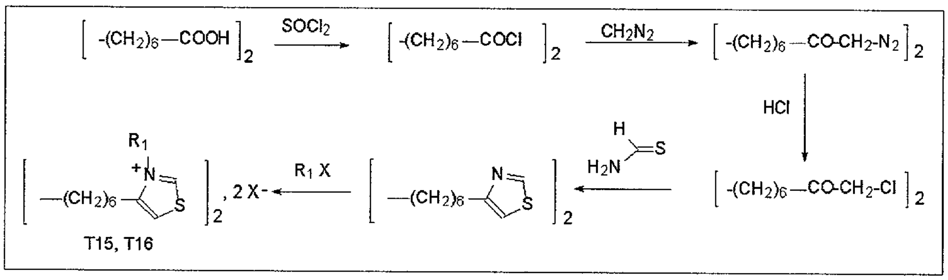
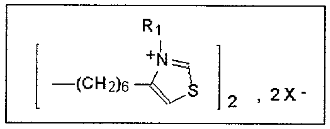


Diagram 6

Tetradecanedioic acid is converted into its chloride (Jayasuriya et al.; J. Amer. Chem. Soc.; 112; 15; 1990; 5844-5850). The latter is treated with diazomethane in order to produce 1,16-bis-diazo-hexadecane-2,15-dione (Canonica et al.; Atti Accad. Naz. Lincei Cl. Sci. Fis. Mat. Nat. Rend.; 8.10; 1951; 479-484), which is treated with HCl and produces 1,16-dichlorohexadecane-2,15-dione (same reference). This compound is then treated with thioformamide under the same conditions as for the synthesis of dodecamethylenebis[5-(4-ethoxycarbonylethyl) thiazole] (Diagram 5, 3rd stage) in order to produce dodecamethylenebis(4-thiazole).

This leads by alkylation on the nitrogen atom (according to the usual process described for T3 or T4) either to dodecamethylenebis[4-(1-methyl)-thiazolium]

diiodide, T15, using iodomethane, or to dodecamethylenebis[4-(1-benzyl)-thiazolium] dibromide, T16, using benzyl bromide.



compounds	R_1	X	IC_{50} (nM)
T15	CH_3-	I	4
T16	C_6H_5-CH_2-	Br	10

Table 9

III. SYNTHESIS OF HALOALKYLAMINES

1) N,N'-dimethyl-N,N'-(5-chloropentyl)-1,16-hexadecane diamine hydrochloride (P1).

a) 5-methylamino-1-pentanol.

10.8 g (0.088 mole) of 5-chloro-1-pentanol is added to 45 ml of an 8M solution of $MeNH_2$ (0.36 mole) in MeOH. The reaction mixture is heated to 100°C in an autoclave for 48 hours. The residue obtained after evaporation of the MeOH is distilled under reduced pressure in order to produce 6.2g (65%) of aminoalcohol.

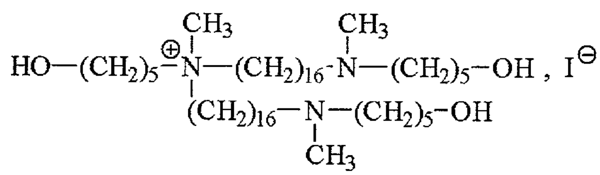
NMR ^{1}H ($CDCl_3$) δ 3.60 (t, 2H, CH_2OH), 2.56 (t, 2H, CH_2NH), 2.40 (s, 3H, CH_3NH), 2.66-1.32 (m, 6H, $(CH_2)_3$).

MS (Electrospray, positive mode) m/z 118 $(M+H]^+$, 100).

b) N,N'-dimethyl-N,N'-(5-hydroxypentyl)-1,16-hexadecanediamine.

0.57g (0.0048 mole) of diisopropylethylamine and 0.58g (0.0045 mole) of 5-methylamino-1-pentanol are added

to 1.08g (0.0022 mole) of diiodohexadecane dissolved in 50 mL of ethanol. The reaction mixture is heated under reflux for 48 hours, the ethanol is then eliminated under reduced pressure. TLC analysis of the residue shows the formation of the expected product and indicates the presence of a small quantity of a very polar compound identified by mass spectrometry as being the quaternary ammonium salt shown in the figure below.



The residue is partially dissolved in water and N,N′-dimethyl-N,N′-(5-hydroxypentyl)-1,16-hexadecane-diamine is extracted in ether with K_2CO_3, leaving the polar contaminant in the water. The ethereal phases are dried over $MgSO_4$, filtered and concentrated under reduced pressure.

NMR ^{1}H ($CDCl_3$) δ 3.60 (t, 4H, CH_2OH), 2.65-2.40 (m, 8H, CH_2-NH-CH_2),), 2.37 (s, 6H, CH_3N), 1.60-1.21 (m, 40H, $2(CH_2)_3$ + $(CH_2)_{14}$).

c) N,N′-dimethyl-N,N′-(5-chloropentyl)-1,16-hexadecanediamine hydrochloride (P1).

The residue obtained above is dissolved in 10 ml of CH_2Cl_2 and 1.7 ml of thionyl chloride is added. The reaction mixture is heated under reflux for 5 hours after which all the volatile products are eliminated under reduced pressure. The residue is triturated in ether until a precipitate appears. The precipitate is filtered then recrystallized from an ethanol-ether mixture in order to produce 0.408 g (32%) of N,N′-dimethyl-N,N′-(5-chloropentyl)-1,16-hexadecanediamine hydrochloride.

NMR ^{1}H ($CDCl_3$) δ 3.48 (t, 4H, CH_2Cl), 3.00-2.80 (m, 8H, CH_2-$NH^+(CH_3)$-CH_2)), 2.70 (d, 6H, CH_3NH^+), 1.86-1.19 (m, 40H, $2(CH_2)_3$ + $(CH_2)_{14}$).

MS (Electrospray, positive mode) m/z 247 (M^{++}, 100), m/z 529/531 ($M^{++}Cl^-$, 20).

2) N,N'-dimethyl-N,N'-(4-chloropentyl)-1,16-hexadecanediamine hydrochloride (P2).

a) 5-methylamino-2-pentanol.

10.59 g (0.10 mole) of γ-valerolactone is added to 60 ml of an 8M solution of $MeNH_2$ (0.48 mole) in MeOH. The reaction mixture is heated at 100°C in an autoclave for 48 hours. The residue obtained after evaporation of the excess $MeNH_2$ under reduced pressure is dissolved in 20 ml of THF and is added to a solution of 6.26 g (0.17 mol) of $LiAlH_4$ in 80 ml of THF for 1 hour in order to obtain a slight reflux. Reflux is maintained for 48 hours, a 5M soda solution is then added dropwise until a whitish suspension is obtained. The reaction mixture is extracted with ether, the ethereal phases are dried over anhydrous $MgSO_4$ and the solvent is eliminated under reduced pressure. The residue obtained is distilled under reduced pressure in order to produce 6.27g (63%) of 5-methylamino-2-pentanol.

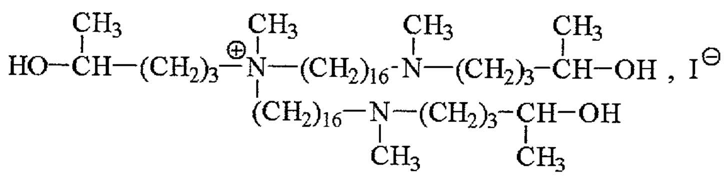
NMR ^{1}H ($CDCl_3$) δ 3.72 (m, 1H, CHOH), 2.76-2.48 (m, 2H, CH_2NH), 2.47 (s, 3H, CH_3NH), 2.66-1.32 (m, 6H, $(CH_2)_3$).

MS (Electrospray, positive mode) m/z 118 ($[M+H]^+$, 100).

b) N,N'-dimethyl-N,N'-(4-hydroxypentyl)-1,16-hexadecanediamine.

0.59g (4.6 mmole) of diisopropylethylamine and 0.61 g (5.8 mmole) of 5-methylamino-2-pentanol are added to 1.10 g (2.3 mmole) of diiodohexadecane dissolved in 50 mL

of ethanol. The reaction mixture is taken to reflux for 48 hours, the ethanol is then eliminated under reduced pressure. TLC analysis of the residue shows the formation of the expected product and indicates the presence of a small quantity of a very polar compound identified by mass spectrometry as being the quaternary ammonium salt shown in the figure below



The residue is partially dissolved in water and N,N'-dimethyl-N,N'-(4-hydroxypentyl)-1,16-hexadecanediamine is extracted in ether with K_2CO_3, leaving the polar contaminant in the water. The ethereal phases are dried over $MgSO_4$, filtered and concentrated under reduced pressure.

NMR ^{1}H ($CDCl_3$) δ 3.70-3.58 (m, 2H, C*H*OH), 2.40-2.24 (m, 8H, CH_2-NH^+(CH_3)-CH_2), 2.16 (s, 6H, CH_3NH^+), 1.66-1.10 (m, 42H, 2(CH_2)$_2$ + 2(CH_3CH) + (CH_2)$_{14}$).

c) N,N'-dimethyl-N,N'-(4-chloropentyl)-1,16-hexadecanediamine hydrochloride (P2).

The residue obtained above is dissolved in 10 ml of CH_2Cl_2 and 2 mL of thionyl chloride is added. The reaction mixture is heated under reflux for 5 hours after which all the volatile products are eliminated under reduced pressure. The residue is triturated in ether until a precipitate appears. The precipitate is filtered then recrystallized from an ethanol-ether mixture in order to produce 0.415g (32%) of N,N'-dimethyl-N,N'-(4-chloropentyl)-1,16-hexadecanediamine hydrochloride.

NMR ^{1}H ($CDCl_3$) δ 4.00 (m, 2H, $CHCl$), 3.00-2.87 (m, 8H, CH_2-$NH^+(CH_3)$-CH_2),), 2.72 (d, 6H, CH_3NH^+), 1.86-1.19 (m, 42H, $2(CH_2)_2$ + $2(CH_3CH)$ + $(CH_2)_{14}$).
MS (Electrospray, positive mode) m/z 247 (M^{++}, 100), m/z 529/531 ($M^{++}Cl^-$, 20).

Study of the pharmacological properties of precursors according to the invention.

A. Antimalarial activity against *P. falciparum in vitro*

The results of the IC_{50} values in nM for the prodrugs of disulphide type (Table 10) and those of thioester type (Table 11) according to the invention, as well as for the corresponding drugs, are presented in Tables 10 and 11 hereafter.

The IC_{50} measurements are determined vis-à-vis *P. falciparum* according to the Desjardins method in which the incorporation of [^{3}H] hypoxanthine (Figure 1) into the nucleic acids is an indicator of cell viability. In each case, optical microscopy controls are carried out.

Table 10

TS prodrug (Ra = S-R)					**T drug**	
R	Z	R_3	name	IC_{50} (nM)	name	IC_{50} (nM)
THF-CH_2-			TS3a	1		
C_3H_7-	-$(CH_2)_{12}$-	HO-CH_2-CH_2-	TS3b	1.3	T3	2 25
C_6H_5-CH_2-		-	TS3c	1.6		
HO-CH_2-CH_2-			TS3d	2 5		
C_3H_7-			TS4b	3.5		
	"	CH_3O-CH_2-CH_2-			T4	0 65

$Et_2N(CH_2)_2$-			TS4c	2.8		
C_3H_7-	″	C_6H_5-COO-$(CH_2)_2$-	TS5	22	/	
C_3H_7-	″	H-	TS6b	3.1	T6	3

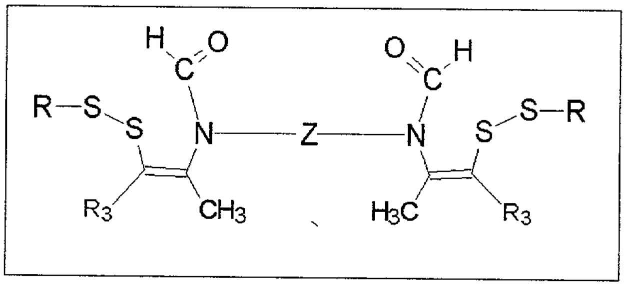
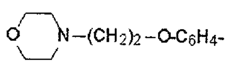
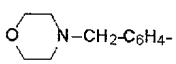
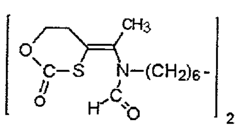


Table 11 A

N-duplicated TE prodrugs (R_a=RCO)				T drug	
R	Z	name	IC_{50} (nM)	name	IC_{50} (nM)
CH_3-	-$(CH_2)_{12}$-	TE4a	14		
$(CH_3)_3C$-	"	TE4b	12		
C_6H_5-	"	TE4c	2		
p-CH_3O- C_6H_4-	"	TE4d	3.4	T4	0.65
	"	TE4e	6.4		
$(C_2H_5)_2N$-CH_2-C_6H_4-	"	TE4f	2.3		
	"	TE4g	2.3		
CH_3OOC- C_6H_4-	"	TE4j	2.7		
C_6H_5-	-$(CH_2)_{16}$	TE8	0 6	T8	1.1
		TE3	2.6	T3	2.25

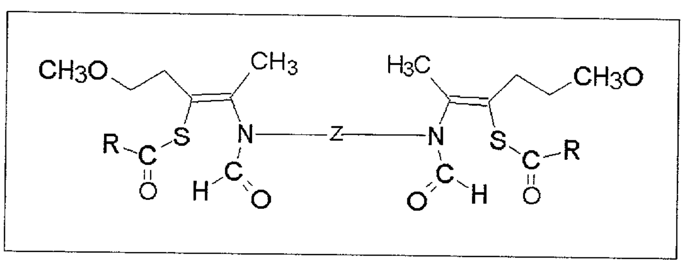
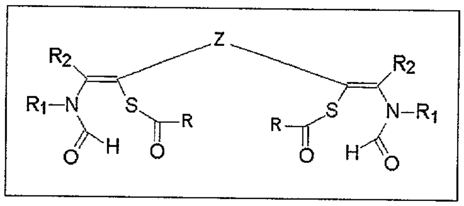


Table 11B

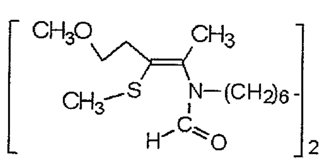
C-duplicated TE prodrugs (R_a=RCO)						**T drug**	
R	R_1	R_2	Z	name	IC_{50} (nM)	name	IC_{50} (nM)
p-CH_3O-C_6H_4-	C_6H_5-CH_2	CH_3-	-$(CH_2)_2O(CH_2)_6O(CH_2)_2$-	TE10	12	T10	2 5
C_6H_5-	CH_3-	CH_2CO_2Et	-$(CH_2)_{12}$-	TE12	16	T12	13



These results show that the IC_{50} values obtained are very low both in the disulphide series and in the thioester series and are of the order of 1 to 14 nM for bis type derivatives with a spacer arm formed by a dodecyl chain.

It can be noted with interest that the IC_{50} value for the ionized cyclized compounds is substantially of the same order of magnitude as that of the corresponding neutral prodrugs.

By way of comparison, the IC_{50} value was measured on a compound which could not be cyclized by enzymatic hydrolysis and corresponding to the formula



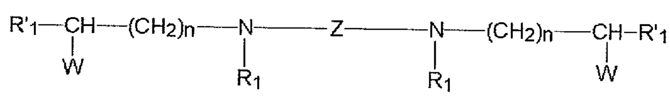
An $IC_{50} > 10^{-5}$ M value which indicates that cyclization is necessary for strong antimalarial activity and also suggests that cyclization is effectively

produced in the presence of serum and/or erythrocytes infected during the 48 hours of the *in vitro* test measuring antimalarial activity.

In Table 12 hereafter, the results of the IC_{50} measurements carried out on haloalkylamines according to the invention are given. These results relate to the prodrugs called P1 and P2 and the corresponding cyclized derivatives G26 and G27 respectively.

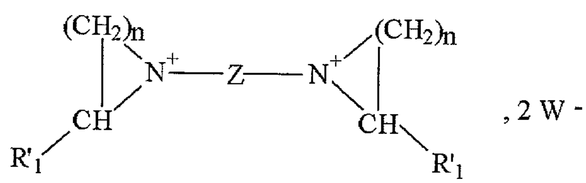
Table 12

Name	Z	R'1	R_1	n	W	IC_{50}(nM)
P1	$-(CH_2)16-$	H	CH_3	4	Cl	1.7
G26	"	"	"	"	I	0.55
P2	"	CH_3	"	3	Cl	0.5
G27	"	"	"	"	I	1.4



(II)

P1, P2



G26, G27

B) Antimalarial activity *in vivo* against a mouse infected by *P. vinckei* and tolerance after administration in acute or semi-chronic conditions.

Table 13 hereafter shows the results obtained with prodrugs according to the invention of disulphide type (TS3b), of thioester type (TE4c, TE4a and TE4e), the

corresponding drug T3 and, by way of comparison, the quaternary ammonium derivative G25.

Table 13

Drug	*In vitro* IC_{50} (nM) (*P. falciparum*)	*In vivo* LD_{50} (mg/kg) (mouse) acute[a]	 semi-chronic[b]	Oral absorption index[c]	*In vivo* ED_{50} (mg/kg) *[TI]* (*P. vinckei*)
G25	**0.6**	**ip 1.27** **po 130**	**1.15** **65**	**87**	**0.22** *[5.2]* **~15** *[4.4]*
T3	**2.25**	**ip 10** **po 700**	**7.5** **160**	**70**	**n.d.**
TS3b	**1.3**	**ip 240** **po 1600**	**90 (32*)** **410**	**6.7**	*~7* $[4.6^{*} < TI \leq 12.8]$ **~180** *[2.3]*
TE4c	**2**	**ip 100** **po ~1000**	$\geq 30^{d}$ **~ 300**	**~10**	**1** $[\geq 30]^{e}$ **30 > x > 1** $[10 < TI < 100]^{e}$
TE4a	**14**	**ip ~50** **po ~1000**	**n.d.**	**~20**	
TE4e	**6.4**	**ip ~50**			

The IC_{50} is the concentration which inhibits by 50 % the *in vitro* growth of *P. falciparum*: the LD_{50} is the lethal dose corresponding to the death of 50 % of the mice and the ED_{50} is the effective dose for inhibiting by 50 % the *in vivo* growth of *P. vinckei* according to a 4-day suppressive test, TI corresponds to the therapeutic index, TI = LD_{50} (semi-chronic)/ED_{50}; ip: intraperitoneal administration; po: per os.

In this table, a) to e) have the following meanings:

a) corresponds to a single dose;

b) corresponds to administration twice per day, for 4 consecutive days;

c) corresponds to the LD_{50} po/LD_{50} ip ratio under acute administration conditions, which ratio is hereafter referred to as "oral absorption index";

d) corresponds to the death of only 25 % of the mice.

"*" The LD_{50} (semi-chronic) decreases in mice infected with malaria;

e) TE4c was used in a 50/50 mixture of PEG/castor oil.

These results show that the prodrugs of the invention have a strong antimalarial activity *in vitro* and *in vivo* as well as good tolerance and high absorption.

C) Pharmacokinetic characteristics and serum level.

C1. Pharmacokinetic parameters in the mouse

The results of the pharmacokinetic parameters after administration by intraperitoneal or oral route in a mouse for a prodrug of disulphide type (TS3b) and a prodrug of thioester type (TE4c) are presented hereafter.

For determination of the serum level, bio-tests are used *ex vivo*: briefly, the medicament is administered to the animal, then repeated blood samples are taken. The *sera* are decomplemented for 30 minutes at 56°C. The active metabolite content is then determined by incubation of different concentrations (dichotomic dilution) of each serum, in the presence of suspensions of erythrocytes infected by *P. falciparum*, according to the DESJARDINS method with [^{3}H] hypoxanthine.

The results are expressed in IS_{50}, which corresponds to the percentage of serum (containing an active metabolite) capable of inhibiting the growth of *P. falciparum* by 50%.

This value is then converted into a serum concentration, (usually expressed in ng/ml) by testing the active compound directly (without passing through the animal), on the same suspension infected by *P. falciparum* and by determining its IC_{50} value (in ng/ml) [serum level = IC_{50}] (in ng/ml) x 100/IS_{50} (in %)].

The results are expressed as the log (serum level of medicaments), as a function of time, which allows the evaluation of the half-time for distribution to the serum compartment $t_{1/2(d)}$; the half-time for elimination of the serum compartment ($t_{½(e)}$); of C_0), corresponding to the serum level originally extrapolated during the elimination phase; the AUC (which indicates the quantity of drug circulating in the blood stream); and the relative bio-availability in the oral route administration method, as against the intraperitoneal route method [AUC (po)/AUC (ip)] which is an indicator of the degree of absorption by oral route.

. Pharmacokinetics of TE4c

Doses of 3 and 50 mg per kg of TE4c are administered to mice by intraperitoneal route and by oral route, which corresponds to $LD_{50}/33$ and $LD_{50}/20$ respectively.

The compound is solubilized in 10% DMSO. Even at these low doses, high serum levels are observed with a diphasic pharmacokinetic profile for both routes. The results are given in Figure 2 which indicates the concentration of seral active metabolite in ng/ml as a function of the time in hours.

In this figure, (-v-) corresponds to ip administration at 3 mg/kg and the curve with (-o-) corresponds to administration po at 50 mg/kg.

In the first phase, a peak is very rapidly observed (in less than two hours) with serum levels which decrease until 4 to 7 hours, then increase and a peak is again observed at around 15 hours, for both administration routes.

These results suggest a rapid first phase during which the prodrug is distributed and enters the serum

compartment. Once in this compartment, the prodrug probably converts to a quaternary ammonium compound.

The second phase can then be carried out in order to determine the pharmacokinetic parameters of the ionized derivative.

If the conversion to an ionized drug is considered to be total, the pharmacokinetic profile can be redrawn on the basis of the IC_{50} of the drug and not on that of the prodrug (see Figure 3, where the legends of the curves are the same as in Figure 2). The semi-logarithmic representation allows the determination of the main pharmacokinetic parameters of the active metabolite (which is considered to be the quaternary ammonium drug T4) for both administration routes (see Figure 4 where the results are redrawn from Figures 2 and 3). The pharmacokinetic parameters are C_0 = 180 ng/ml, $t_{1/2}$ = 12 hours, AUC = 3.3 µg.hr/ml after ip administration at 3 mg/kg, and C_0 = 130 ng/ml, $t_{1/2}$ = 12 hours 30 minutes, AUC = 2.7 µg.h/ml after oral administration at 50 mg/kg. Under these conditions, the relative bioavailability is 5%.

In another series of experiments, the pharmacokinetics were studied at higher doses of TE4c (10 mg/kg ip and 150 mg/kg po).

A diphase profile was also observed at higher serum levels and in this case the second peak occurs slightly later (at around 23 hours) as shown in Figures 5A and 5B.

<u>Estimation of the pharmacokinetic parameters: by oral route,</u>

C_0 = 1 µg/ml and $t_{1/2}$ at around 10 hours.

<u>. Pharmacokinetics of TS3b</u>

TS3b was administered to mice at doses of 50 and 400 mg/kg, respectively by intraperitoneal route and by oral route (approximately $LD_{50}/3$).

High serum levels are observed forming peaks 2 to 4 hours after the administration of drugs (Figure 6). The pharmacokinetic parameters were then estimated from the semi-logarithmic representation of the serum concentration (calculated on the basis of the IC_{50} of TS3b as a function of time).

After intra-peritoneal administration at 50 mg/kg, a C_0 of 2.75 µg/ml is obtained with $t_{1/2}$ of approximately 6 hours.

By oral route at 400 mg/kg, C_0 is 1.8 µg/ml, indicating very high serum levels. The apparent $t_{1/2}$ is 13 hours. Such a difference in the $t_{1/2}$ between the two administration routes could indicate a difference in the metabolization of the prodrug.

The pharmacokinetic profile observed in Figure 6 could reflect only the first phase of a diphase profile, corresponding to an absorption/distribution phase, such as that observed for the prodrug of thioester type TE4c.

Another series of experiments was carried out to check the existence of a diphase profile, with blood samples taken up to 30 hours after the administration of the drug by ip route (see Figure 7 which gives the serum concentration of TS3b in ng/ml as a function of time in hours).

It can be observed that a diphase profile is indeed obtained, although incomplete.

The first phase is characterized by a peak at approximately 2 hours with a serum levels decreasing until 10 hours; between 10 and 24 hours, only a slight increase is observed followed by a sharp increase between

24 hours and 30 hours. This probably corresponds to a first phase in which the prodrug is distributed and enters the serum compartment.

This first phase appears less early than for TE4C considered above.

Once in the serum compartment, the conversion of the prodrug into a quaternary compound occurs. Very long term pharmacokinetic experiments must be carried out in order to evaluate the pharmacokinetic parameters of the second phase (i.e. the ionized derivative corresponding to T3) which led to the use of the monkey as a model.

Pharmacokinetic parameters in the monkey.

TS3b is administered by intramuscular route to *Macaca fascicularis* monkeys at 4 mg/kg (see Figures 8A and 8B which give the concentration in TS3b in ng/ml as a function of time in hours).

Repeated blood samples are taken up to 76 hours and a clear diphase profile is observed.

The first phase very rapidly forms a peak in less than two hours with a serum levels decreasing up to 10 hours, then increasing and forming a peak again at around 30 hours.

As indicated above, this can correspond to the first rapid phase for which the prodrug is distributed and enters the serum compartment.

Once in this compartment, the prodrug converts to quaternary ammonium compounds.

The second phase can then be carried out in order to determine the pharmacokinetic parameters of the ionized derivative corresponding to T3.

If it is considered that the complete conversion to the ionized drug has occurred, the pharmacokinetic profile can be redrawn above on the basis of the IC_{50} of

the drug and not on the basis of the prodrug (see Figure 8A). High serum levels are observed, C_0 is 1.4 μg/ml and $t_{1/2}$ around 17 hours.

These results taken together demonstrate the pharmacokinetic properties of the different products appropriate for making use of the different pharmacological activities claimed.

Antimalarial activity against *Plasmodium falciparum* in the *Aotus* monkey.

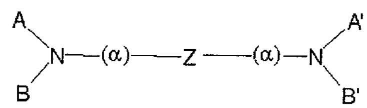
3 *Aotus* monkeys were infected with *P. falciparum* (FVO strain). When the blood parasitemia reached 1% (2 monkeys) or 6% (1 monkey), treatment by intramuscular route at a rate of 2 injections per day of TE4c (2mg/kg), for 8 days, was carried out. In each case, the blood parasitemia was completely eliminated and no further occurrence was observed in the 6 months following the treatment. These results indicate the compound's effective capacity for curing human malaria caused by *P. falciparum*.

Antibabesiasis activities of the compounds

The products TE4c, TS3b and P1 were also evaluated *in vitro* for their activities against Babesia divergens and *B. canis*. In both cases, the compounds TE4c, TS3b and P1 showed themselves to be particularly active (IC_{50} < 20 nM). These results indicate a strong antibabesia activity for this type of compounds.

CLAIMS

1/ Precursors of drugs with an anti-malarial action, characterized in that it concerns quaternary bis-ammonium salts and that they correspond to general formula (I)

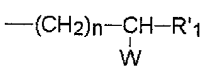


(I)

in which

- A and A' are identical to or different from one another and represent

· either, an A_1 and A'_1 group respectively, of formula



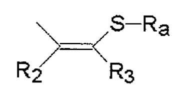
where n is an integer from 2 to 4; R'_1 represents a hydrogen atom, a C1 to C5 alkyl radical, optionally substituted by an aryl radical (in particular a phenyl radical), a hydroxy, an alkoxy, in which the alkyl radical comprises from 1 to 5 C, or aryloxy (in particular phenoxy); and W represents a halogen atom chosen from chlorine, bromine or iodine, or a nucleofuge group, such as the tosyl $CH_3-C_6H_4-SO_3$, mesityl CH_3-SO_3, CF_3-SO_3, $NO_2-C_6H_4-SO_3$ radical,

· or an A_2 group which represents a formyl -CHO, or acetyl $-COCH_3$ radical,

- B and B' are identical to or different from one another and represent

· either the B_1 and B'_1 groups respectively, if A and A' represent A_1 and A'_1 respectively, B_1 and B'_1 representing an R_1 group which has the same definition as R'_1 above, but cannot be a hydrogen atom,

· or the B_2 and B'_2 groups respectively, if A and A' represent A_2, B_2 or B'_2 being the R_1 group as defined above, or a group of formula

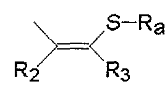


in which -Ra represents an RS- or RCO- group, where R is a linear, branched or cyclic C1 to C6 alkyl radical, optionally substituted by one or more hydroxy or alkoxy (or aryloxy) groups or an amino group and/or a -COOH or COOM group, where M is a C1 to C3 alkyl; a phenyl or benzyl radical, in which the phenyl radical is optionally substituted by at least one C1 to C5 alkyl or alkoxy radical, these being optionally substituted by an amino group, or by a nitrogenous or oxygenous heterocycle, a -COOH or -COOM group; or a $-CH_2$-heterocycle group, with 5 or 6 elements, nitrogenous and/or oxygenous; R_2 represents a hydrogen atom, a C1 to C5 alkyl radical, or a $-CH_2$-COO-alkyl (C1 to C5) group; and R_3 represents a hydrogen atom, a C1 to C5 alkyl or alkenyl radical, optionally substituted by -OH, a phosphate group, an alkoxy radical, in which the alkyl radical is C1 to C3, or an aryloxy radical; or an alkyl (or aryl), carbonyloxy group; or also R_2 and R_3 together form a ring with 5 or 6

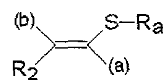
carbon atoms; R and R_3 can be linked to form a ring of 5 to 7 atoms (carbon, oxygen, sulphur)

- $\underline{\alpha}$ represents

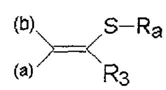
. either a single bond, when $\underline{A}$ and $\underline{A'}$ represent $\underline{A_1}$ and $\underline{A'_1}$: or when $\underline{A}$ and $\underline{A'}$ represent $\underline{A_2}$, i.e. a $-CHO$ or $-COCH_3$ group, and $\underline{B_2}$ and $\underline{B'_2}$ represent



. or, when $\underline{A}$ and $\underline{A'}$ represent A_2 and $\underline{B_2}$ and $\underline{B'_2}$ represent $\underline{R_1}$, a group of formula



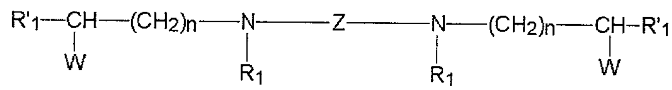
or a group of formula



in which (a) represents a bond towards $\underline{Z}$ and (b) a bond towards the nitrogen atom.

- $\underline{Z}$ represents a C6 to C21 alkyl radical, in particular C13 to C21 optionally with insertion of one or more multiple bonds, and/or one or more O and/or S heteroatoms, and/or one or more aromatic rings, and the pharmaceutically acceptable salts of these compounds.

2/ Precursors according to claim 1, characterized in that it relates to haloalkylamines, corresponding to general formula (II)



(II)

in which $\underline{R_1}$, $\underline{R'_1}$, $\underline{W}$, $\underline{n}$ and $\underline{Z}$ are as defined in claim 1.

3/ Precursors according to claim 1, characterized in that Z represents a C13 to C21 alkyl radical.

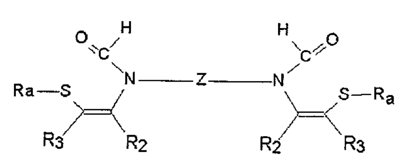
4/ Precursors according to claim 3, characterized in that $\underline{Z}$ represents a $-(CH_2)_{16}-$ group.

5/ Precursors according to any one of claims 2 to 4, characterized in that $\underline{R_1}$ is a methyl radical.

6/ Precursors according to any one of claims 2 to 5, characterized in that $\underline{R_1}$ is a methyl radical and $\underline{R'_1}$ is either a hydrogen atom, or a methyl radical, and $\underline{W}$ is a chlorine atom.

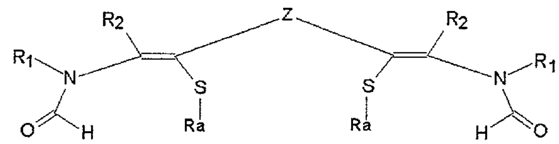
7/ Precursors according to any one of claims 2 to 6, characterized in that they are chosen from N, N'-dimethyl-N,N'-(5-chloropentyl)-1,16-hexadecanediamine hydrochloride, or N, N'-dimethyl-N,N'-(4-chloropentyl)-1,16-hexadecanediamine hydrochloride.

8/ Precursors according to claim 1, characterized in that it relates to precursors of thiazolium corresponding to general formula (III).



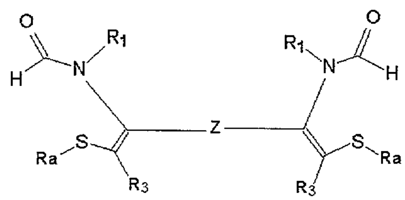
(III)

or to general formula (IV)



(IV)

or to general formula (V)



(V)

in which $\underline{R_a}$, $\underline{R_1}$, $\underline{R_2}$, and $\underline{Z}$ are as defined in claim 1.

9/ Precursors according to claim 8, characterized in that they correspond to formula III in which $\underline{R_a}$ represents an RCO- radical.

10/ Precursors according to claim 9, characterized in that they are chosen from

N,N'-diformyl-N,N'-di[1-methyl-2-S-thiobenzoyl-4-methoxybut-1-enyl]-1, 12-diaminododecane,

N,N'-diformyl-N,N'-di[1-methyl-2-S-(p-diethylaminomethylphenyl-carboxy)thio-4-methoxybut-1-enyl]-1,12-diaminododecane,

N,N'-diformyl-N,N'-di[1-methyl-2-S-(p-morpholino-methylphenylcarboxy)-thio-4-methoxybut-1-enyl]-1,12-diaminododecane,

N,N'-diformyl-N,N'-di[1-methyl-2-S-thiobenzoyl-4-methoxybut-1-enyl]-1,16-diaminohexadecane and

N,N'-diformyl-N,N'-di[1(2-oxo-4,5-dihydro-1,3-oxathian-4-ylidene)ethyl]1,12-diaminododecane

11/ Precursors according to claim 8, characterized in that $\underline{R}_a$ represents <u>RS-</u>.

12/ Precursors according to claim 11, characterized in that they are chosen from

N,N'-diformyl-N,N'-di[1-methyl-2-tetrahydrofurfuryl-methyldithio-4-hydroxybut-1-enyl]-1,12-diaminododecane,

N,N'-diformyl-N,N'-di[1-methyl-2-propyl-dithio-4-hydroxybut-1-enyl]-1,12-diaminododecane,

N,N'-diformyl-N,N'-di[1-methyl-2-benzyl-dithio-4-hydroxybut-1-enyl]-1.12 diaminododecane,

N,N'-diformyl-N,N'-di[1-methyl-2-(2-hydroxyethyl)-dithio-4-hydroxybut-1-enyl]-1,12-diaminododecane (TS3d)

N,N'-diformyl-N,N'-di[1-methyl-2-propyldithio-4-methoxybut-1-enyl]-1,12-diaminododecane,

and N,N'-diformyl-N,N'-di[1-methyl-2-propyldithio-ethenyl]-1,12-diaminododecane.

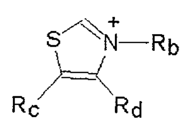
13/ Precursors according to claim 8, characterized in that they correspond to formula IV and are chosen from 2,17-(N,N'-diformyl-N,N'-dimethyl)diamino-3,16-S-thio-p-methoxybenzoyl-6,13-dioxaoctadeca-2,16-diene, 2,17-(N,N'-diformyl-N,N'-

dibenzyl)diamino-3,16-S-thio-p-methoxybenzoyl-6,13-dioxaoctadeca-2,16-diene, ethyl 3,18 (N,N'-diformyl-N,N'-dimethyldiamino-4,17-S-thiobenzoyl-eicosa-3,17-dienedioate (TE12), ethyl 3,18-(N,N'-diformyl-N,N'-dibenzyl)diamino-4,17-S-thiobenzoyl-eicosa-3,17-dienedioate.

14/ Precursors according to claim 8, characterized in that they correspond to formula (V) and are chosen from 2,15-(N,N'-diformyl-N,N'-dimethyl)diamino-1,16-S-thiobenzoyl-hexadeca-1,15-diene.

2,15-(N,N'-diformyl-N,N'-dibenzyl)diamino-1,16-S-thio-benzoyl-hexadeca-1,15-diene.

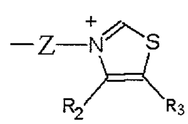
15/ The cyclized derivatives corresponding to the precursors of thiazolium according to any one of claims 8 to 14 corresponding to general formula (VI)



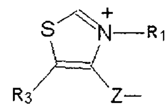
(VI)

in which

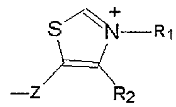
. $\underline{R}_b$ represents $\underline{R}_1$ or $\underline{T}$, $\underline{T}$ representing the group of formula



. $\underline{R}_d$ represents $\underline{R}_2$ or $\underline{P}$, $\underline{P}$ representing the group of formula



.R_c represents R_3 or U, U representing the group of formula



R_1, R_2, R_3 and Z being as defined in claim 1,

it being understood that R_b = T, if R_c = R_3 and R_d = R_2; R_d = P, if R_c = R_3 and R_b = R_1; and R_c = U, if R_b = R_1, and R_d = R_2.

16/ Process for obtaining precursors of thiazolium of general formula (III) to (IV) according to claim 8, characterized in that it comprises the reaction in basic medium of a thiazole derivative of formula (VI).

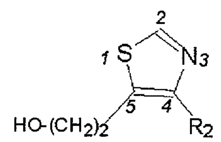
17/ Process according to claim 16, characterized in that in order to obtain the compounds in which R_a = RCO-, a derivative of thiazolium of formula (VI) is reacted with an RCOR' derivative, where R is as defined in claim 1 and R' is a halogen atom, and in order to obtain the compounds in which R_a = RS-, said thiazolium derivatives of formula (VI) are reacted with a thiosulphate derivative RS_2O_3Na.

18/ Process according to claim 16 or 17, characterized in that

- in order to obtain the compounds of formula (III) a thiazole derivative suitably substituted with an alkyl dihalide is reacted, under reflux in an organic

solvent, the opening of the thiazolium ring then takes place in basic medium, and by the action either of R-COCl, or of $RS_2O_3N_a$,

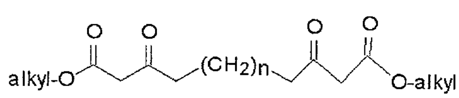
- in order to obtain the compounds of formula IV, which comprise an oxygen in the Z chain, a thiazole derivative of general formula (VII)



(VII)

is reacted with an alkane dihalide, in basic medium, then the addition of R_1X, the reaction medium being advantageously taken to reflux in an organic solvent, in particular alcoholic such as ethanol, for a duration sufficient to obtain the quaternization of the nitrogen atom of the thiazole by fixing R_1, the opening of the thiazolium ring then being obtained in basic medium, then by the action either of R-COCl, or of RS_2O_3Na,

- in order to obtain the compounds of formula (IV) not comprising oxygen in the Z chain, a compound of structure

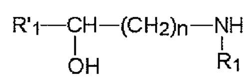


is firstly synthesized by reacting an alkyl acetoacetate with NaH, followed by alkylation, then the addition of a dihalogenoalkane, the compound obtained

then being dibrominated, then thioformamide is added and, after reflux for several days, R_1X, which leads, after renewed reflux for several days, to a thiazolium, the opening of which is then carried out in basic medium, then the action of R-COCl or of $R\text{-}S_2O_3N_a$,

- in order to obtain the compounds of formula (V) not comprising oxygen in the Z chain, a $Z(CO\text{-}CH_2\ X)_2$ compound is reacted with $CH(=S)NH_2$, then R_1X is added, the opening of the thiazolium ring then being carried out in basic medium, then by adding R-COCl or $R\text{-}S_2O_3N_a$.

19/ Process for obtaining haloalkylamines according to claim 1, characterized in that it comprises the alkylation of an amino alcohol of formula



by an alkyl α,ω-dihalide X-Z-X, which leads to a bis-aminoalcohol treated with a compound capable of releasing the W group.

20/ Pharmaceutical compositions, characterized in that they contain an effective quantity of at least one precursor as defined in any one of claims 1 to 14, or at least one compound according to claim 15, in combination with an inert pharmaceutical vehicle.

21/ Pharmaceutical compositions according to claim 20, characterized in this that they can be administered by oral route, by injectable route, or also by rectal route.

22/ Compositions according to claim 20 or 21 for the treatment of infectious diseases, in particular

malaria or babesiosis in man or animals, characterized in that they include an effective quantity of the precursors according to any one of claims 1 to 14, or at least one compound according to claim 15.

23/ Use of at least one compound according to any one of claims 1 to 14 or according to claim 15, to manufacture medicaments for the treatment of infectious diseases, in particular maleria or babesiosis in humans or animals.

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FIGURE 1

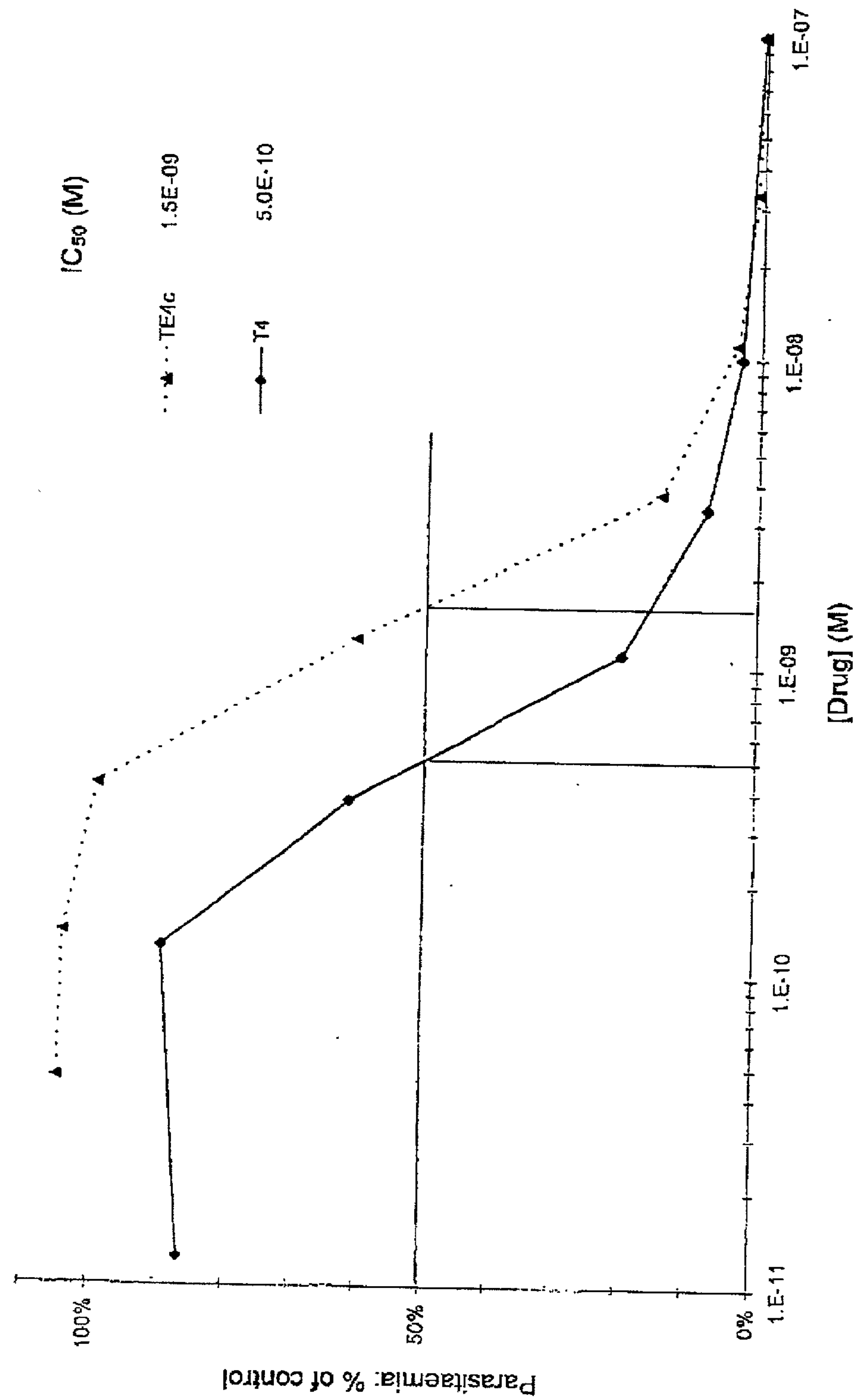

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FIGURE 2

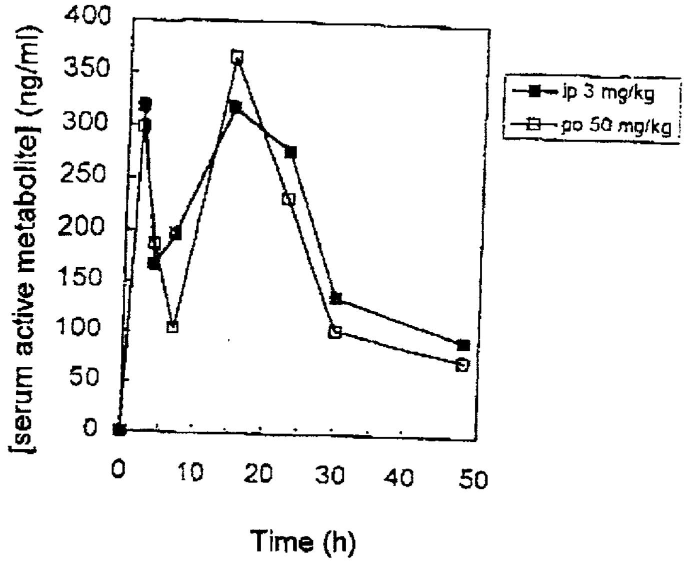

FIGURE 3

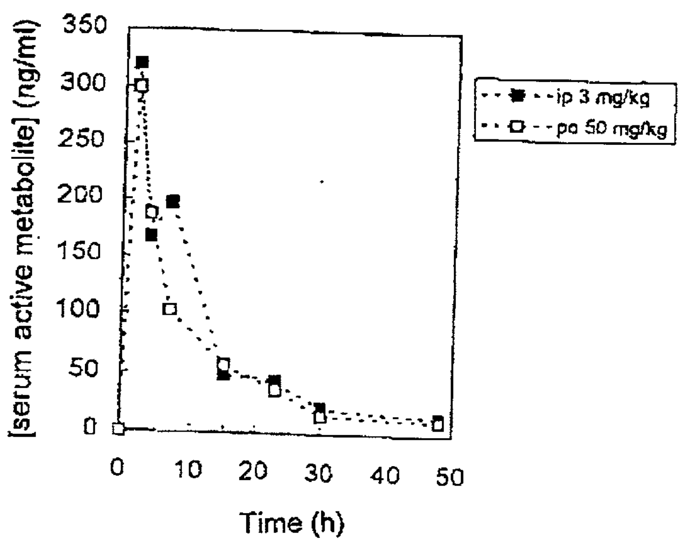

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FIGURE 4

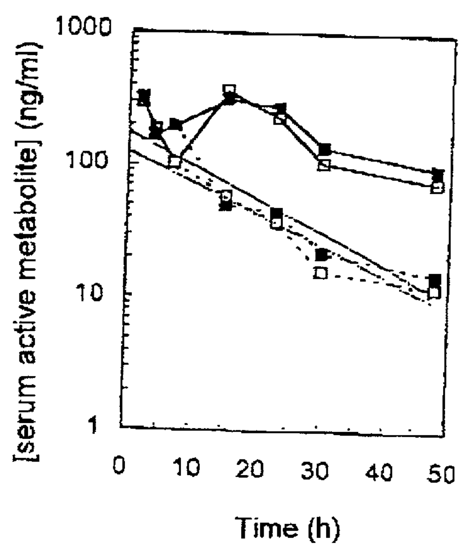

1000
100
10
1
[serum active metabolite] (ng/ml)
0
10
20
30
40
50
Time (h)

FIGURE 5A

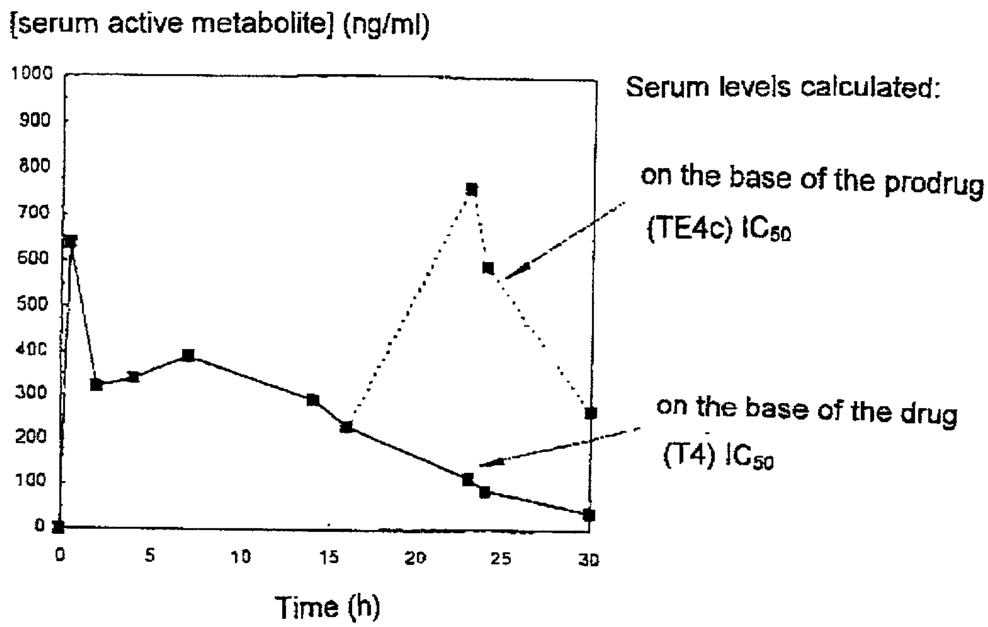


FIGURE 5B

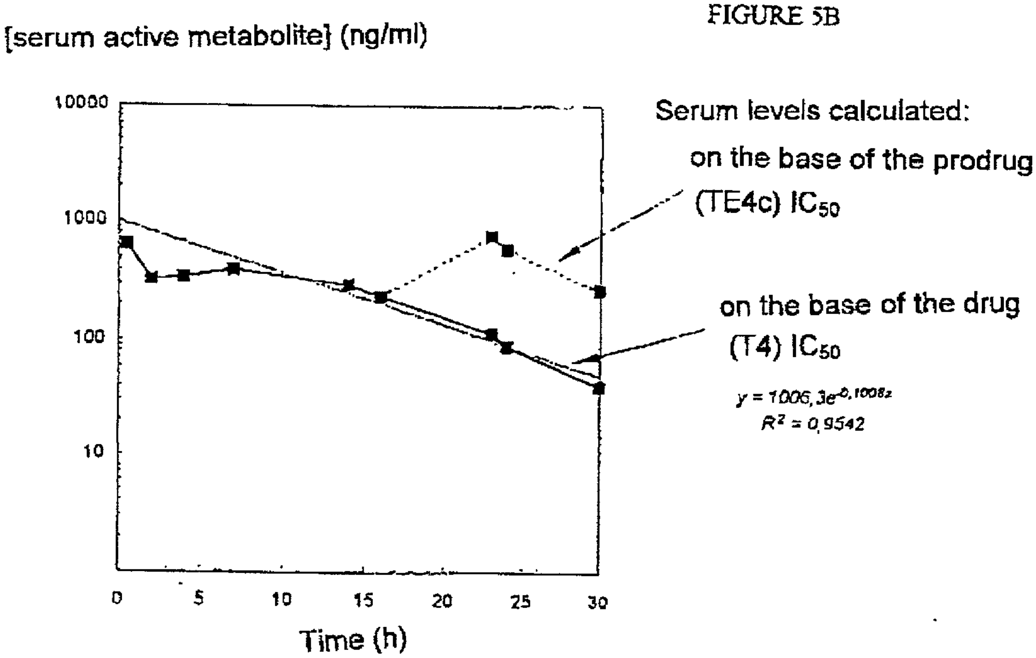


FIGURE 6

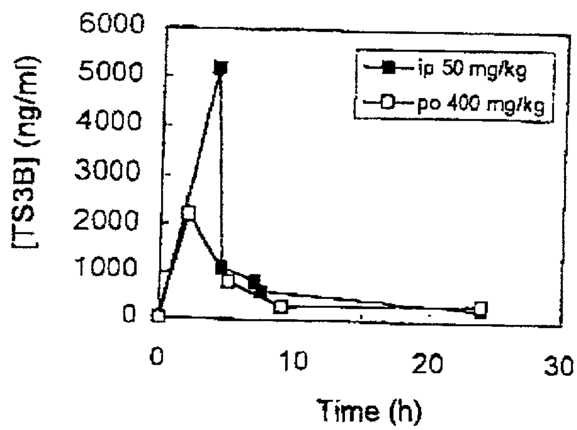


FIGURE 7

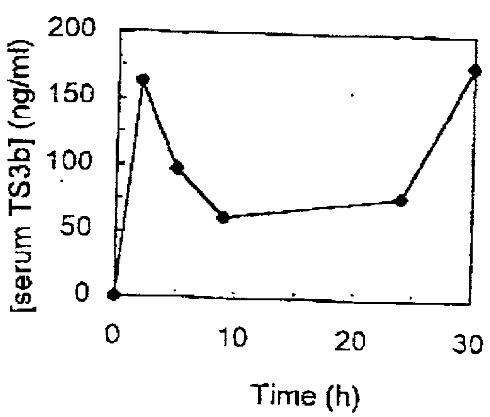


FIGURE 8A

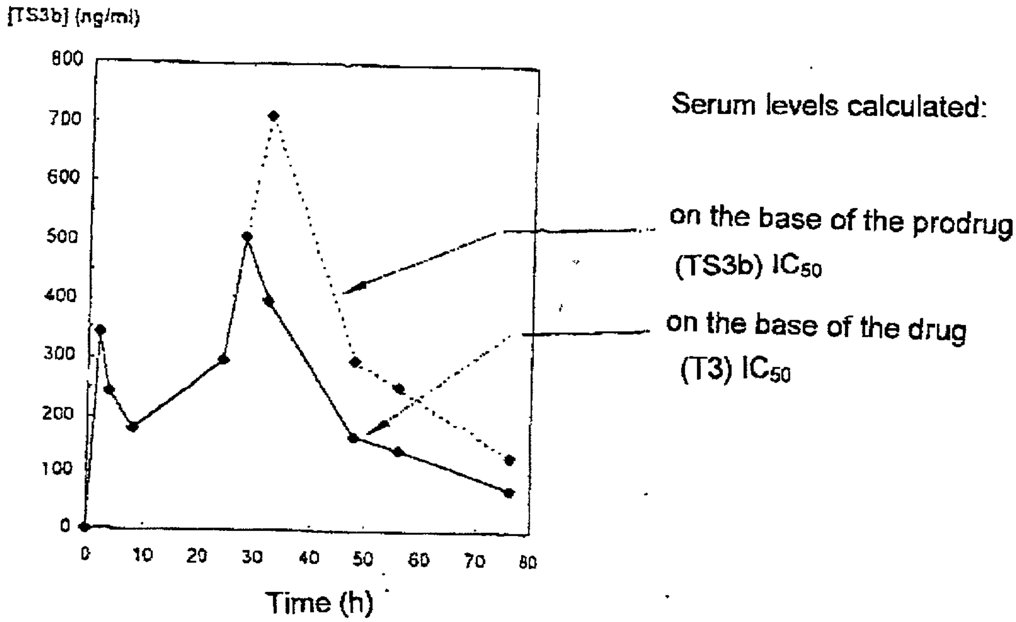
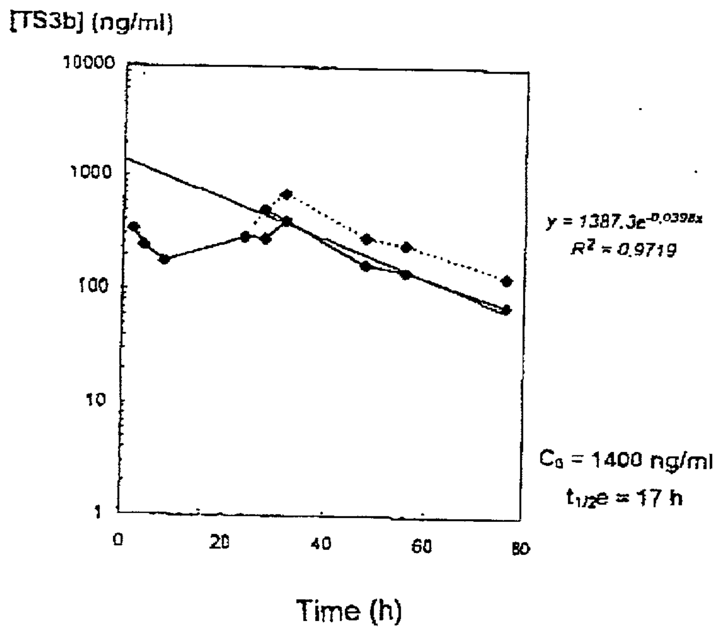


FIGURE 8B



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Nixon & Vanderhye P.C (10/99)
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RULE 63 (37 C.F.R. 1.63)
INVENTORS DECLARATION FOR PATENT APPLICATION IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

As a below named inventor, I hereby declare that my residence, mailing address and citizenship are as stated below next to my name and I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:
QUATERNARY BIS-AMMONIUM SALT PRECURSORS AND THEIR USES AS PRODRUGS HAVING AN ANTIPARASITIC ACTIVITY
the specification of which (**check applicable box(s)**):

☐ is attached hereto
☐ was filed on ______ as U.S. Application Serial No. ______ (Atty Dkt. No. 1721-45)
☐ was filed as PCT International application No. PCT/FR00/02122 on 21/07/2000
and (if applicable to U.S. or PCT application) was amended on October 30, 2001

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose to the Patent Office all information known to me to be material to patentability as defined in 37 C.F.R. 1.56. I hereby claim foreign priority benefits under 35 U.S.C. 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed or, if no priority is claimed, before the filing date of this application:
Priority Foreign Application(s):

Application Number	Country	Day/Month/Year Filed
99 09 471	FR	21/07/1999

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

Application Number	Date/Month/Year Filed

I hereby claim the benefit under 35 U.S.C. 120/365 of all prior United States and PCT international applications listed above or below.

Prior U.S./PCT Application(s): Application Serial No.	Day/Month/Year Filed	Status: patented pending, abandoned
PCT/FR00/02122	21/07/2000	

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon. And on behalf of the owner(s) hereof, I hereby appoint **NIXON & VANDERHYE P.C., 1100 North Glebe Rd., 8th Floor, Arlington, VA 22201-4714, telephone number (703) 816-4000 (to whom all communications are to be directed)**, and the following attorneys thereof (of the same address) individually and collectively owner's/owners' attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith and with the resulting patent: Larry S. Nixon, 25640; Arthur R. Crawford, 25327; James T Hosmer, 30184; Robert W Faris, 31352; Richard G. Besha, 22770; Mark E. Nusbaum, 32348; Michael J. Keenan, 32106; Bryan H Davidson, 30251; Stanley C. Spooner, 27393; Leonard C. Mitchard, 29009; Duane M. Byers, 33363; Jeffry H. Nelson 30481; John R. Lastova, 33149; H. Warren Burnam, Jr. 29366; Mary J. Wilson, 32955; J. Scott Davidson 33489; Alan M. Kagen, 36178; Robert A Molan, 29834; B. J. Sadoff, 36663; James D Berquist, 34776; Updeep S. Gill, 37334; Michael J Shea, 34725; Donald L. Jackson, 41090; Michelle N. Lester, 32331; Frank P. Presta, 19828; Joseph S. Presta, 35329; Joseph A. Rhoa, 37515; Raymond Y Mah, 41426; Chris Comuntzis, 31097; Gary T. Tanigawa, 43180. I also authorize Nixon & Vanderhye to delete any attorney names/numbers no longer with the firm and to act and rely solely on instructions directly communicated from the person, assignee, attorney, firm, or other organization sending instructions to Nixon & Vanderhye on behalf of the owner(s).

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1-00
1. Inventor's Signature: [signature] Date: 27 January 2002
Inventor: Henri (first) MI VIAL (last) French (citizenship)
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2-00
2. Inventor's Signature: [signature] Date: 28 January 2002
Inventor: Marie-Laure (first) MI ANCELIN (last) French (citizenship)
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☒ *See attached sheet(s) for additional inventor(s) information!!*

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Serial No.

(Domestic Non-Assigned/Foreign)

3-00

3. Inventor's Signature:				Date: 28 janvier 2002
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4. Inventor's Signature:				Date: 28 Janvier 2002
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5-00

5. Inventor's Signature:				Date: 28 January 2002
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6. Inventor's Signature:				Date: 28 Janvier 2002
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FOR ADDITIONAL INVENTORS, check box ☐ and attach sheet with same information and signature and date for each

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